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Single Dose Pharmacokinetics of 5 Formulations of Lithium: a Controlled Comparison in Healthy Subjects

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The single dose pharmacokinetics of 4 lithium preparations (Camcolit-400, Priadel, Liskonum, Litarex) and a new micro-encapsulated formulation were compared in normal volunteers using a balanced cross-over design. The data show an inverse relationship between rate of release and bioavailability. The pharmacokinetic characteristics of Camcolit-400 and Priadel were similar; both showed earlier and greater peak serum concentrations than the other 3. The new formulation, which accounted for most of the significant variance, had the slowest rate of release and the lowest bioavailability. Statistical analysis showed significant differences between the 5 preparations for *C*-max, *T*-max, 12-h serum levels, AUC and urinary excretion, but not for the 24-h serum levels. No serious untoward side-effects were noted.

Introduction

For the effective and safe application of lithium in the treatment and prophylaxis of manic-depressive illness detailed knowledge of its pharmacokinetic properties is required. Unlike most other psychotropic drugs, the therapeutic range for lithium is narrow. The minimum serum level required for clinical effect is about 0·4 mmol/l while the level at which toxic symptoms may occur is 1·5 mmol/l (Stokes, 1971; Srinivasan and Hullin, 1980; Brown, 1980). A relationship between serum concentration and non-toxic side-effects has also been claimed (Persson, 1977; Mellerup *et al.*, 1979). Consequently, attempts have been made to formulate slow-release lithium preparations which would minimize side-effects by reducing the maximum serum concentrations. Furthermore, compliance might be improved by decreasing the number of daily doses required.

There has been some lack of agreement regarding the relative plasma pharmacokinetic properties of the various lithium preparations currently available in the British Isles (Coppen *et al.*, 1969; Tyrer *et al.*, 1976; Bennie *et al.*, 1977; Wall *et al.*, 1978; Tyrer, 1982).

Some of the previous studies appear to have a number of methodological shortcomings. These can be categorized as: 1. relating to the population under study; 2. the experimental design.

Firstly, although in most studies either patients or normal volunteer subjects were used, in some both were investigated. Within the patient population a variety of different diagnostic categories have been included: affective disorders are the most frequent, but patients with schizophrenia, schizo-affective illness and alcohol-

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ism have also been involved (Shaw *et al.*, 1974; Tyrer *et al.*, 1976; Bennie *et al.*, 1977). Where patients with mood disorders were the sole participants only 3 studies provide information on the affective state of the patients at the time of investigation (Crammer *et al.*, 1974; Tyrer *et al.*, 1976; Johnson, 1982) and only in 1 were they all apparently at the same mood level (Johnson, 1982). We do not know sufficient about the effect of diagnosis and mood on lithium pharmacokinetics to rule out possible interference in such studies. Furthermore, the demographic characteristics and the physical status of the population studied are only infrequently described, and information on concomitant drug intake is often lacking.

Secondly, in most studies it is apparent that all subjects did not take each preparation, thereby introducing another potential source of variation, particularly as population size was often quite small. Four studies comparing 2 preparations did use a cross-over design (Shaw *et al.*, 1974; Johnson *et al.*, 1979; Tyrer *et al.*, 1982; Johnson *et al.*, 1982) and one study, which compared 4 preparations, used a balanced latin square design (Wall *et al.*, 1978). The frequency of blood sampling was generally 1-hourly or 2-hourly, and the total number taken ranged from 5 to 17. Such relative infrequency of sampling prejudices against obtaining accurate values for *C*-max (maximum serum concentration) and *T*-max (time to maximum serum concentration).

The aim of the present study was to compare, with a balanced design, the single dose pharmacokinetics of 4 lithium preparations (Camcolit-400, Priadel, Liskonum, Litarex) and of a new micro-encapsulated formulation of lithium carbonate (referred to here as "New Capsule") in a group of normal male subjects, all of whom took all 5 preparations.

Method

(a) *Subjects*

Twelve normal male volunteer subjects aged 27 to 45 years (mean 31·8 ± 5·4) participated. Physical examination and laboratory investigation revealed no abnormality, in particular their serum creatinine levels and urinalysis were all within normal limits. None were taking other medication during the trial. Their mean weight was 77·9 kg (± 7·8).

(b) *Procedure*

Subjects were assigned in random order to take each of the 5 preparations in turn according to a balanced design under single-blind conditions. For each preparation tablets were taken from the same production batch.

Having fasted overnight, 27·0 mmol (30·5 mmol in the case of Liskonum) of lithium was administered orally with 200 ml of cold water. A standard breakfast was allowed 30 min later. Fluid and food intake was recorded during the study day. Side-effects, either volunteered or elicited, were scored for severity on a 4-point scale and their time of appearance and duration noted.

Blood for lithium estimation was sampled through an indwelling venous cannula according to the following schedule:

(a) before lithium administration;
(b) half-hourly for 8 hours after administration;
(c) hourly for the following 4 hours;
(d) a further sample was taken by venepuncture at 24 hours.

Urine was collected prior to administration and on each subsequent micturition during the study day. The volume of urine voided was recorded and an aliquot removed for lithium estimation.

All the lithium concentrations were measured by flame photometry in the same laboratory.

The mean serum concentrations and mean percentage recovered in the urine for each preparation were calculated. The urea under the 24-hour serum curve (AUC) was estimated with the trapezoidal rule. Analysis of variance was used to estimate the level of significance of differences in these parameters between the 5 preparations. Where appropriate, a paired *t*-test was done to estimate the significance of the difference between 2 preparations. To calculate the elimination half-life the mean serum concentrations over time for each preparation were plotted on semi-log graph paper and a straight line drawn through the points of the elimination phase of the decay curve. The elimination half-life was then read from this line. This parameter, because it was calculated from mean values only, was not subject to analysis of variance.

Results

The relevant pharmacokinetic data are presented in Table 1 and Fig. 1. In general they indicate that as the rate of release is reduced, as shown by lower serum peaks and longer half-lives, bioavailability decreases, as shown by the smaller AUC and percentage recovered in the urine.

Priadel and Camcolit are similar, although Priadel has a slightly lower *C*-max, AUC and percentage recovered in the urine than Camcolit; these differences are not statistically significant. Both show an earlier peak concentration time than the other 3 preparations and the maximum plasma level is greater.

Liskonum led to a slightly lower and later peak. Litarex had a different pharmacokinetic profile, the time of peak lithium concentration was earlier than Liskonum but much lower in amplitude; the area under the curve was also lower.

The New Capsule appeared to be less well absorbed than the others; the *C*-max, the AUC and the proportion recovered from the urine was significantly lower than the other preparations.

Side-effects were neither frequent nor serious. Out of 60 study days, side-effects were reported on 21 occasions. These were equally distributed between upper gastrointestinal tract systems (nausea, indigestion), lower gastrointestinal tract systems (loose bowel motion, diarrhoea) and the central nervous system (drowsiness). On a 4-point scale of severity 18 were rated 2, and 3 rated 3. There was a tendency for higher peak serum concentrations to be associated with nausea or mild drowsiness, with delayed release being more likely to lead to loose bowel motions or diarrhoea. The incidence of side-effects for each preparation is as follows: Liskonum—7, New Capsule—5, Litarex—4, Priadel—4 and Camcolit—1.

TABLE 1

	Camcolit	*Priadel*	*Liskonum*	*Litarex*	*New Cap.*	*Analysis of variance*
	Mean [±]					
C-Max (mmol/l)	0·63 (0·16)	0·60 (0·16)	0·55 (0·12)	0·41 (0·12)	0·31 (0·10)	$p < 0·001$
T-Max (h)	2·5 (1·2)	2·5 (1·1)	5·0 (1·4)	3·25 (1·2)	8·0 (7·6)	$p < 0·005$
12-h conc. (mmol/l)	0·30 (0·05)	0·30 (0·06)	0·34 (0·05)	0·27 (0·06)	0·25 (0·04)	$p < 0·005$
24-h conc. (mmol/l)	0·24 (0·05)	0·24 (0·05)	0·24 (0·05)	0·21 (0·05)	0·23 (0·03)	N.S.
AUC (mmol/l/h)	8·6 (1·4)	8·4 (1·7)	8·6 (1·4)	7·0 (1·6)	6·0 (1·2)	$p < 0·005$
% recovered urine	52% (8·7)	48% (9·7)	48% (13·2)	46% (8·9)	37% (11·3)	$p < 0·025$
Elimination half-life (h)	18	20	21	22	33	

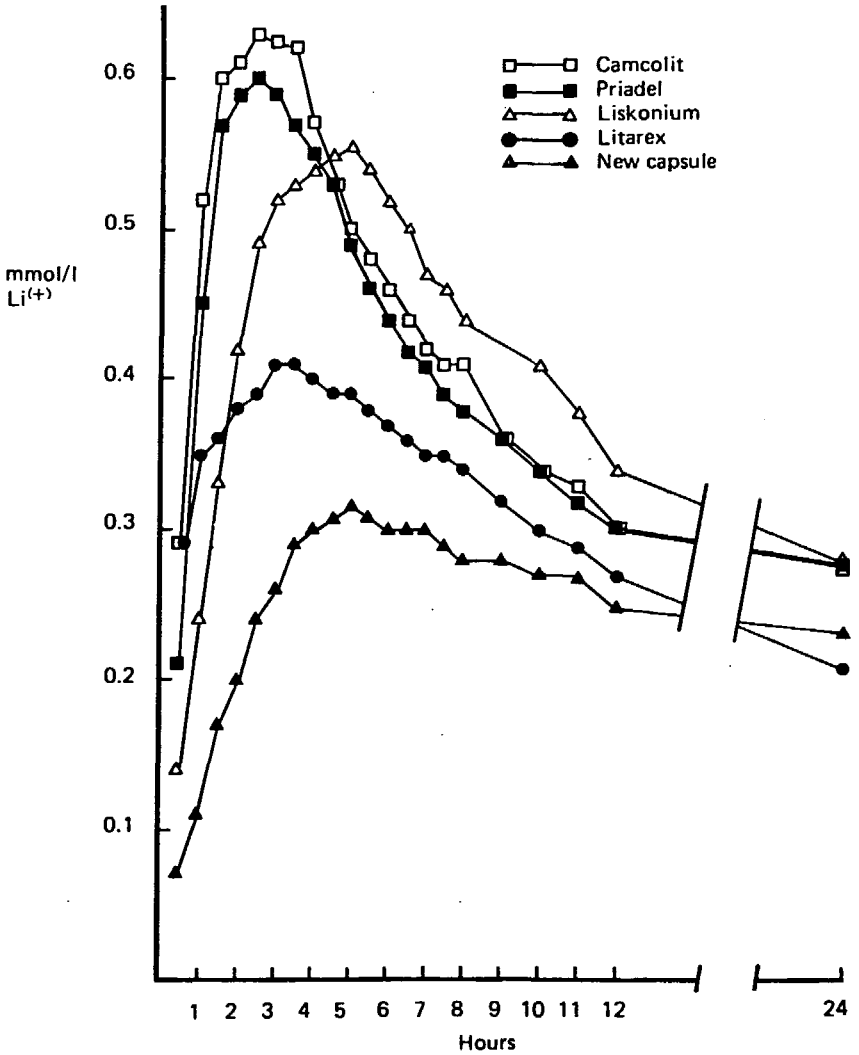

FIG. 1. Mean serum lithium concentrations, N = 12 for each preparation.

Discussion

Of the 5 preparations examined, Priadel has been the most intensively studied hitherto. Early reports (Coppen, 1969) suggested it had clear-cut, slow-release properties, with a *T*-max of approximately 6 hours. However, that value was based on infrequent blood sampling; and no other lithium preparation was included as a reference. Subsequent studies have most commonly compared Priadel with Camcolit, a British Pharmacopoeia formulation. Tyrer (1976) found them to be

relatively similar, but when a cross-over design was used (Tyrer, 1978) Priadel appeared to have a slower rate of release, especially over the first 2 hours after administration. Hullin (1977) substituted Camcolit-400 for Priadel in patients without obtaining any differences in blood levels. By contrast, other studies comparing Priadel with "standard" formulations have shown it to have delayed-release characteristics (Wall, 1978; Johnson, 1979; Johnson, 1982).

One possible cause of this seeming discrepancy may lie in the fact that some of the studies used Camcolit-250, whereas others (usually the more recent) used Camcolit-400. In addition, as Scott (1977) has pointed out, all standard British Pharmacopoeia formulations of lithium may not have the same bioavailability. Tyrer (1978) refers to unpublished work suggesting that Camcolit-400 may have some delayed release properties compared to Camcolit-250. The findings of the present study would be in keeping with this view. Similarly, Bennie (1978) found Priadel to have a longer half-life than Camcolit-250, but found no significant differences between Priadel and Camcolit-400.

We could not confirm the earlier report of a *T*-max value of around 6 hours for Priadel (Coppen, 1969). This could be explained by a change in the formulation of Priadel. In keeping with this possibility the urinary excretion of an earlier batch of Priadel showed it to yield a recovery of 59% compared to a recovery of 87% from a newer batch (Amdisen, 1975). These findings suggest notable differences in bioavailability. Amdisen (1975) also described a similar pattern of excretion for the newer Priadel and Litarex. We, however, found Litarex to have a different excretory profile yielding a lower proportion of the total taken in the urine.

Apart from that discrepancy our pharmacokinetic findings for Litarex are in keeping with others (Tyrer, 1978; Tyrer *et al.*, 1982), and the flattened shape of the serum curve is similar to that reported by Amdisen (1975); Litarex had a lower *C*-max and a smaller AUC than either Camcolit-4000 or Priadel.

This is the first comparative pharmacokinetic study to include Liskonum. The only published work to date found a *T*-max similar to ours of 4·5 hours, which indicates some delayed release (Mengech, 1984). As the dose of 450 mg used in that study differs markedly from ours, more detailed pharmacokinetic comparisons are precluded; compounding ethnic and dietary differences may also exist but these remain unproven. Furthermore, in our study the slightly higher dose of Liskonum compared to the other 4 preparations needs to be considered when interpreting the data.

The New Capsule contributed most to the significant variance between the 5 preparations over a wide range of pharmacokinetic parameters, yet its 24-hour serum concentrations were not significantly different from the others. This fact, and the shape of the mean serum concentration curve, suggests that it is possible to devise a lithium formulation which approximates to being reliably sustained-release. Unfortunately, this is at the expense of bioavailability, 2 subjects achieving unacceptably low serum levels over 24 hours.

Despite a higher and earlier peak plasma level of lithium with Priadel and Camcolit, this was not accompanied by a greater number of side-effects, although the nature of the side-effects experienced differed from those associated with the slower release preparations. Four subjects when taking Priadel and 1 when taking Camcolit suffered from nausea. Liskonum, on the other hand, caused side-effects

in 7 subjects, the most frequent being diarrhoea. This pattern of side-effects was similar in the 2 other longer-acting preparations.

In summary, Priadel and Camcolit-400 have similar pharmacokinetic profiles: both are relatively rapidly and effectively absorbed and have half-lives of 18–20 hours. Liskonum is absorbed more slowly and reaches a lower peak serum level; the AUC, percentage recovered in the urine and the elimination half-life are similar to those of Priadel and Camcolit-400. Litarex by contrast has less bioavailability than the 3 available formulations; it was less completely absorbed than Liskonum although absorption was more rapid.

The New Capsule is truly sustained-release, but as has already been stated, this was at the expense of a significant lessening in bioavailability and an increased incidence of lower gastrointestinal tract symptoms.

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FACTORS ASSOCIATED WITH A GOOD RESPONSE TO LITHIUM IN AGGRESSIVE MENTALLY HANDICAPPED SUBJECTS

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(Final form, June 1984)

Abstract

Tyrer, Stephen P., Angela Walsh, Derek E. Edwards, Tom P. Berney and D. Alan Stephens. Factors associated with a good response to lithium in aggressive mentally handicapped subjects. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1984, 8 (4-6): 751-755.

1. Twenty-five (25) mentally handicapped in-patient adults with persistent aggressive behaviour took part in a double-blind crossover trial lasting 5 months comparing the effects of lithium with placebo on aspects of aggressive behaviour.
2. All patients were receiving neuroleptic and/or anticonvulsant drugs which were continued during the trial.
3. Seventeen (17) of the patients showed greater improvement during the lithium phase compared to placebo.
4. Multiple regression analysis was carried out to determine which of 17 background variables were related to outcome.
5. The following factors were associated with a good response to lithium: less than one aggressive episode per week before starting treatment, overactivity, stereotypic behaviour, female sex and epilepsy.
6. No patient became toxic during the investigation although lithium levels were maintained within the therapeutic range (0.5-0.8 mmol/l).

Keywords: aggression, epilepsy, lithium, mental handicap

Abbreviations: electroencephalogram (EEG); full blood count (FBC)

Introduction

Lithium has been found to be an effective treatment in controlling impulsive aggressive episodes in prisoners (Sheard et al. 1976). It has also been employed in mentally handicapped patients with assaultive behaviour with some success (Worrall et al. 1975; Dale 1980). Self-mutilatory behaviour may also be helped (Cooper and Fowlie 1973). Lithium toxicity has been a problem in some of these studies and insufficient numbers have been treated with the drug to determine which patients benefit.

This study aimed to compare the comparative efficacy of lithium with inactive medication in the treatment of aggressive episodes. The factors associated with a good response to the drug were also determined.

Methods

Patient Population. Twenty-six (26) mentally handicapped in-patients (17 males, 9 females) at two hospitals in Northumberland with at least 4 episodes of aggressive behaviour recorded each month over the previous six months, entered a trial to compare the effect of adding lithium or inactive medication to their existing neuroleptic and/or

anticonvulsant treatment, which was kept constant during the period of study. Their ages ranged from 14 to 50 years (mean 27). No patient was included who had evidence of recurrent depressive or manic mood changes, but other psychiatric diagnoses were not a contra-indication to entry into the trial. The relatives of all patients accepted into the trial gave informed consent if this was impossible to obtain from the patient concerned.

Drug Administration. Lithium was given in the form of lithium carbonate (Camcolit) in 250 mg tablets. Each patient took 500 mg of Camcolit before the study and 24 hours later blood was taken for measurement of serum lithium level. According to the serum lithium level obtained the maintenance dose of lithium predicted to obtain a steady-state serum lithium level of between 0.5 and 0.8 mmol/l was determined according to a pre-existing nomogram (Tyrer and Shaw 1982). Blood was taken for serum lithium estimation every two weeks during the trial. The lithium levels were known only to the technician involved in the investigation who informed the clinician of all deviations from the advised therapeutic range of lithium (0.5-0.8 mmol/l). In order to maintain blindness, every result indicating a high or low lithium level was given with a similar reading for a patient receiving placebo. Camcolit was given in two or three divided doses during the day. The study design is shown in Table 1.

Table 1
Study design

	Phase 1	Phase 2	Phase 3
Group A	Placebo	Lithium	Placebo
Group B	Placebo	Placebo	Lithium
Time period	1 month	2 months	2 months
	← Serum lithium every 2 weeks →		
Investigations	Thyroxine FBC Creatinine Urea Electrolytes Lithium loading dose EEG	Thyroxine FBC Creatinine Urea EEG	Thyroxine FBC Creatinine Urea EEG

Assessment Instruments. Laboratory investigations carried out during the investigation are shown in Table 1.

The nursing staff in the wards involved completed a rating scale assessing 20 behavioural items in the areas of aggression, hyperactivity, antisocial behaviour and destructiveness, adapted from a similar scale by El Kaisi and McGuire (1974). The psychiatrist recorded his own rating on 10 cm visual analogue scales concerned with 13 behavioural items. These were completed after consultation with the nursing staff and perusal of the nurses' rating scales. In addition, all seclusion episodes and accident reports were noted during the period of the study.

Data Analysis. An initial principal component analysis of the 13 psychiatric ratings established the dimensionality of the data to be between five and seven dimensions. Factor analyses on the weeks in each phase of the study (9 analyses) showed that the factors could be rotated (Cliff, 1966) to give reasonable agreement on most of the factors used. Six common factors were assumed based on each patient week in phase 1 and these accounted for 73% of the variation. Multiple regression analyses were then carried out and showed a significant regression of each factor up to 7 of the 17 background variables.

Results

Sample Attrition

One (1) patient was withdrawn from the study before completion of the trial and another patient was only able to complete one month of treatment in each phase because of concern by the senior nursing staff, not because of clinical deterioration. This last patient has been included in the analysis.

Efficacy

Seventeen (17) of the 25 patients who completed the trial showed improvement during the lithium phase compared to placebo. Of the six factors 5 improved during the lithium period, although only one factor, rhythmic movement and stereotypic behaviour showed a significant difference with lithium. One factor, hyperactivity and noisiness, showed no difference whatsoever between the lithium and placebo phases (Fig. 1). The multiple correlation of placebo-lithium factor scores on 17 background variables are indicated in Table 2.

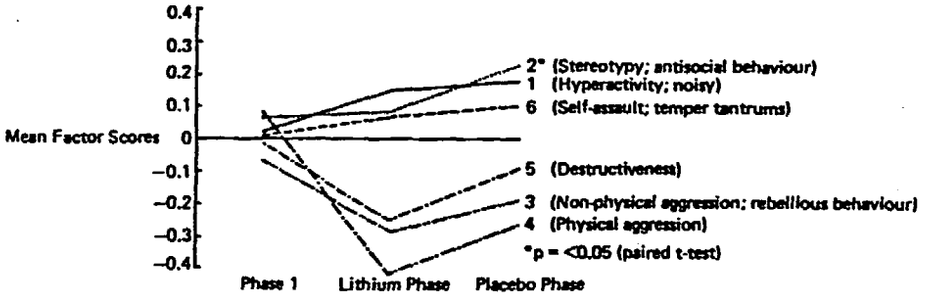

Fig. 1. Change in behaviour during three phases of trial. Deviations from zero line indicate improvement: those inclining towards this line indicate deterioration.

Table 2
Multiple correlation of placebo-lithium factor scores on background variables

Factor		Most highly correlated background variable	Correlation coefficient (r)
Non-physical aggression	(3)	Sex	0.55**
Destructiveness	(5)	Treatment group	0.46*
Rhythmic movement	(2)	Brain damage	−0.45*
Self-assault	(6)	Aggression provoked	−0.39*
Physical aggression	(4)	Frequency of aggression	−0.35*

Positive correlation indicates a higher value of the background variable is associated with a better response to lithium
*$p < 0.05$ **$p < 0.01$

Safety

No patient became toxic or required reduction in lithium dosage because of side-effects during the investigation. Of the eight epileptic patients in the study only one showed an increase in fit frequency during the study, from one to two episodes per month. The lithium loading dose test used was highly accurate at predicting subsequent steady-state lithium levels - the correlation between the initial loading dose value and the predicted steady-state lithium level was 0.79.

Discussion

The results confirm earlier reports that lithium is an effective drug in the control of both aggressive and self-mutilatory behaviour in mentally handicapped subjects. The improvement was considerable in eight patients. However, unlike earlier studies none of the 25 patients involved in this investigation became toxic, despite the fact that 8 of the patients were epileptic and 16 subjects had evidence of cerebral impairment to some degree. The absence of toxicity is probably related to the low dosage lithium policy in our study although lithium levels were within the therapeutic range. It is unlikely that the frequent blood monitoring helped a great deal as no patient had to have his lithium dosage reduced because of a progressively increasing serum lithium level.

The statistical significance of the multiple regression analysis is unclear because of the number of factors involved and the relatively small number of patients. The results suggest that the following factors are associated with a good response to lithium: less than one aggressive episode per week before starting treatment, overactivity, stereotypic behaviour, female sex, and epilepsy. The degree of mental handicap, mood, periodicity of aggressive outbursts, serum lithium level, and nature of accompanying medication were unrelated to improvement with the drug. Although overactive patients improved with the drug with regard to their aggressive episodes their degree of overactivity was not altered by lithium treatment.

Conclusions

The results indicate that lithium is effective in controlling aggression in mentally handicapped adults, and patients with epilepsy and brain damage can be safely treated with benefit. Improvement is less likely to occur in socially withdrawn male patients with frequent aggressive outbursts.

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RECOMMENDATION OF THE

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LITHIUM

INDICATIONS

Acute mania.

Prophylaxis of recurrent affective disorders.

DOSAGE

ACUTE MANIA

(As stated in the data sheets) - dose to be given in divided doses.

PROPHYLAXIS OF RECURRENT AFFECTIVE DISORDERS

600-1200 mg/day given in divided doses.
Clinical improvement is usually associated with serum concentrations of 0.5 mmol or above. Toxic symptoms are usually associated with concentrations exceeding 1.5 mmol.

USE IN ELDERLY

500-1000 mg/day given in divided doses.

Toxic symptoms are likely with serum concentrations above 1.0 mmol.

USE IN CHILDREN Not recommended.

MEASUREMENT OF SERUM LITHIUM CONCENTRATIONS

Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. On initiation of therapy serum concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals thereafter. Additional measurements should be made if signs of lithium toxicity occur (see below), on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs

As bioavailability varies from product to product (particularly with regard to retard or slow release preparations) a change of product should be regarded as initiation of new treatment. Blood levels should therefore be monitored weekly until re-stabilisation is achieved.

More frequent monitoring is required if patients are receiving diuretics.

CONTRAINDICATIONS

Renal disease

Cardiovascular disease

Addison's disease

Breast Feeding

WARNINGS AND ADVERSE EFFECTS (Contd)	Renal function should be routinely monitored in patients with polyuria and polydypsia. Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmc Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist. Long term treatment with lithium is frequently associated with disturbances of thyroid function including goitre, hypothyroidism and thyrotoxicosis. Mild cognitive impairment may occur during long term use. Hypercalcaemia, hypermagnesaemia, hyperparathryoidism and an increase in antinuclear antibodies have also been reported. Exacerbation of psoriasis may occur.
SIGNS OF IMPENDING TOXICITY.	Appearance or aggravation of gastrointestinal symptoms, muscle weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle twitching and a large output of dilute urine. At blood levels above 2-3 mmol/l, there is increasing disorientation, seizures, coma and death.
PHARMACY	[redacted]
LEGAL STATUS	Lithium carbonate is available on prescription only, except where the maximum dose is the equivalent of 5 mg of the base or less, and the maximum daily dose is 15 mg of the base or less.

USE IN PREGNANCY

There is epidemiological evidence that the drug may be harmful in human pregnancy. Should the use of lithium be unavoidable, close monitoring of serum concentrations should be made throughout the pregnancy and during parturition.

PRECAUTIONS

Pre-treatment and periodic routine clinical monitoring is essential. This should include assessment of renal function, urine analysis, assessment of thyroid function and cardiac function, especially in patients with cardio-vascular disease.

Patients should be euthyroid before the initiation of lithium therapy.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Warnings and Adverse Effects). Patients should also be warned to report if polyuria or polydypsia develops. Episodes of nausea and vomiting or other conditions leading to salt/water depletion(including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Elderly patients are particularly liable to lithium toxicity.

DRUG INTERACTIONS

Lower doses of lithium may be needed during diuretic therapy as lithium clearance is reduced.

Raised plasma levels of ADH may occur during treatment.

Symptoms of nephrogenic diabetes are particularly prevalent in patients receiving concurrent treatment with tri/tetracyclic antidepressants.

Serum lithium concentrations may increase during concomitant therapy with indomethacin or tetracycline.

WARNINGS AND ADVERSE EFFECTS

Long-term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum clinically effective dose of lithium should always be used. Patients should be maintained on lithium after 3-5 years only if, on assessment, benefit persists.

RECOMMENDATION OF THE

COMMITTEE ON THE REVIEW OF MEDICINES NOVEMBER 1979

LITHIUM

INDICATIONS

Acute mania.

Prophylaxis of recurrent affective disorders.

DOSAGE

ACUTE MANIA

(As stated in the data sheets) - dose to be given in divided doses.

PROPHYLAXIS OF RECURRENT AFFECTIVE DISORDERS

600-1200 mg/day given in divided doses.
Clinical improvement is usually associated with serum concentrations of 0.5 mmol or above. Toxic symptoms are usually associated with concentrations exceeding 1.5 mmol.

USE IN ELDERLY

500-1000 mg/day given in divided doses.

Toxic symptoms are likely with serum concentrations above 1.0 mmol.

USE IN CHILDREN Not recommended.

MEASUREMENT OF SERUM LITHIUM CONCENTRATIONS

Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. On initiation of therapy serum concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals thereafter. Additional measurements should be made if signs of lithium toxicity occur (see below), on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs.

As bioavailability varies from product to product (particularly with regard to retard or slow release preparations) a change of product should be regarded as initiation of new treatment. Blood levels should therefore be monitored weekly until re-stabilisation is achieved.

More frequent monitoring is required if patients are receiving diuretics.

CONTRAINDICATIONS

Renal disease

Cardiovascular disease

Addison's disease

Breast Feeding

USE IN PREGNANCY

There is epidemiological evidence that the drug may be harmful in human pregnancy. Should the use of lithium be unavoidable, close monitoring of serum concentrations should be made throughout the pregnancy and during parturition.

PRECAUTIONS

Pre-treatment and periodic routine clinical monitoring is essential. This should include assessment of renal function, urine analysis, assessment of thyroid function and cardiac function, especially in patients with cardio-vascular disease.

Patients should be euthyroid before the initiation of lithium therapy.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Warnings and Adverse Effects). Patients should also be warned to report if polyuria or polydypsia develope. Episodes of nausea and vomiting or other conditions leading to salt/water depletion(including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Elderly patients are particularly liable to lithium toxicity.

DRUG INTERACTIONS

Lower doses of lithium may be needed during diuretic therapy as lithium clearance is reduced.

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Serum lithium concentrations may increase during concomitant therapy with indomethacin or tetracycline.

WARNINGS AND ADVERSE EFFECTS

Long-term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum clinically effective dose of lithium should always be used. Patients should be maintained on lithium after 3-5 years only if, on assessment, benefit persists.

WARNINGS AND ADVERSE EFFECTS (Contd)

Renal function should be routinely monitored in patients with polyuria and polydypsia.

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol.

Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist.

Long term treatment with lithium is frequently associated with disturbances of thyroid function including goitre, hypothyroidism and thyrotoxicosis.

Mild cognitive impairment may occur during long term use.

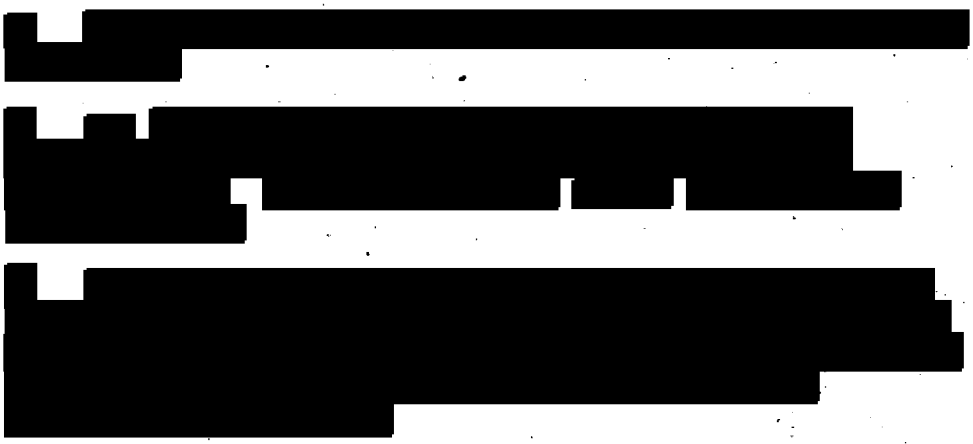
Hypercalcaemia, hypermagnesaemia, hyperparathryoidism and an increase in antinuclear antibodies have also been reported.

Exacerbation of psoriasis may occur.

SIGNS OF IMPENDING TOXICITY

Appearance or aggravation of gastrointestinal symptoms, muscle weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle twitching and a large output of dilute urine. At blood levels above 2-3 mmol/l, there is increasing disorientation, seizures, coma and death.

PHARMACY



LEGAL STATUS

Lithium carbonate is available on prescription only, except where the maximum dose is the equivalent of 5 mg of the base or less, and the maximum daily dose is 15 mg of the base or less.

GE

RECOMMENDATION OF THE

COMMITTEE ON THE REVIEW OF MEDICINES

LITHIUM

INDICATIONS

Acute mania.

Prophylaxis of recurrent affective disorders.

DOSAGE

ACUTE MANIA

(As stated in the data sheets) - dose to be given in divided doses.

PROPHYLAXIS OF RECURRENT AFFECTIVE DISORDERS

600-1200 mg/day given in divided doses.
Clinical improvement is usually associated with serum concentrations of 0.5 mmol or above. Toxic symptoms are usually associated with concentrations exceeding 1.5 mmol.

USE IN ELDERLY

500-1000 mg/day given in divided doses.

Toxic symptoms are likely with serum concentrations above 1.0 mmol.

USE IN CHILDREN Not recommended.

MEASUREMENT OF SERUM LITHIUM CONCENTRATIONS

Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. On initiation of therapy serum concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals thereafter. Additional measurements should be made if signs of lithium toxicity occur (see below), on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs.

As bioavailability varies from product to product (particularly with regard to retard or slow release preparations) a change of product should be regarded as initiation of new treatment. Blood levels should therefore be monitored weekly until re-stabilisation is achieved.

More frequent monitoring is required if patients are receiving diuretics.

CONTRAINDICATIONS

Renal disease

Cardiovascular disease

Addison's disease

Breast Feeding

WARNINGS AND ADVERSE EFFECTS (Contd)

Renal function should be routinely monitored in patients with polyuria and polydypsia.

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol.

Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist.

Long term treatment with lithium is frequently associated with disturbances of thyroid function including goitre, hypothyroidism and thyrotoxicosis.

Mild cognitive impairment may occur during long term use.

Hypercalcaemia, hypermagnesaemia, hyperparathryoidism and an increase in antinuclear antibodies have also been reported.

Exacerbation of psoriasis may occur.

SIGNS OF IMPENDING TOXICITY

Appearance or aggravation of gastrointestinal symptoms, muscle weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle twitching and a large output of dilute urine. At blood levels above 2-3 mmol/l, there is increasing disorientation, seizures, coma and death.

PHARMACY

[redacted]

LEGAL STATUS

Lithium carbonate is available on prescription only, except where the maximum dose is the equivalent of 5 mg of the base or less, and the maximum daily dose is 15 mg of the base or less.

USE IN PREGNANCY

There is epidemiological evidence that the drug may be harmful in human pregnancy. Should the use of lithium be unavoidable, close monitoring of serum concentrations should be made throughout the pregnancy and during parturition.

PRECAUTIONS

Pre-treatment and periodic routine clinical monitoring is essential. This should include assessment of renal function, urine analysis, assessment of thyroid function and cardiac function, especially in patients with cardiovascular disease.

Patients should be euthyroid before the initiation of lithium therapy.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Warnings and Adverse Effects). Patients should also be warned to report if polyuria or polydypsia develope. Episodes of nausea and vomiting or other conditions leading to salt/water depletion(including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Elderly patients are particularly liable to lithium toxicity.

DRUG INTERACTIONS

Lower doses of lithium may be needed during diuretic therapy as lithium clearance is reduced.

Raised plasma levels of ADH may occur during treatment.

Symptoms of nephrogenic diabetes are particularly prevalent in patients receiving concurrent treatment with tri/tetracyclic antidepressants.

Serum lithium concentrations may increase during concomitant therapy with indomethacin or tetracycline.

WARNINGS AND ADVERSE EFFECTS

Long-term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum clinically effective dose of lithium should always be used. Patients should be maintained on lithium after 3-5 years only if, on assessment, benefit persists.

Jan. 1980. Minutes of Nov. CRM

ANNEXE 6

NOT FOR PUBLICATION

COMMITTEE ON THE REVIEW OF MEDICINES 6.11.79 TO CRM 79/M6

RECOMMENDATION

LITHIUM

INDICATIONS

Acute mania

Prophylaxis of recurrent affective disorders.

DOSAGE

ACUTE MANIA

(As stated in the data sheets) - dose to be given in divided doses.

PROPHYLAXIS OF RECURRENT AFFECTIVE DISORDER

600-1200 mg/day given in divided doses. Clinical improvement is usually associated with serum concentration of 0.5 mmol or above. Toxic symptoms are usually associated with concentrations exceeding 1.5 mmol.

USE IN ELDERLY

500-1000 mg/day given in divided doses. Toxic symptoms are likely with serum concentrations above 1.0 mmol.

USE IN CHILDREN Not recommended.

MEASUREMENT OF SERUM LITHIUM CONCENTRATIONS

Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. On initiation of therapy serum concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals therafter. Additional measurements should be made if signs of lithium toxicity occur (see below), on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs.

As bioavailability varies from product to product (particularly with regard to retard or slow release preparations) change of product should be regarded as initiation of new treatment. Blood levels should therefore be monitored weekly until re-stabilisation is achieved.

More frequent monitoring is required if patients are receiving diuretics.

CONTRAINDICATIONS

Renal disease

Cardiovascular disease

Addison's disease

Breast Feeding

IN PREGNANCY

There is epidemiological evidence that the drug may be harmful in human pregnancy. Should the use of lithium be unavoidable, close monitoring of serum concentrations should be made throughout the pregnancy and during parturition.

PRECAUTIONS

Pre-treatment and periodic routine clinical monitoring is essential. This should include assessment of renal function, urine analysis, assessment of thyroid function and cardiac function, especially in patients with cardio-vascular disease.

Patients should be euthyroid before the initiation of lithium therapy.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Warnings and Adverse Effects). Patients should also be warned to report if polyuria or polydypsia develop. Episodes of nausea and vomiting or other conditions leading to salt/water depletion (including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Elderly patients are particularly liable to lithium toxicity.

DRUG INTERACTIONS

Lower doses of lithium may be needed during diuretic therapy as lithium clearance is reduced.
Raised plasma levels of ADH may occur during treatment.
Symptoms of nephrogenic diabetes are particularly prevalent in patients receiving concurrent treatment with tri/tetracyclic antidepressants.
Serum lithium concentrations may increase during concomitant therapy with indomethacin or tetracycline.

WARNINGS AND ADVERSE EFFECTS

Long-term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum clinically effective dose of lithium should always be used. Patients should be maintained on lithium after 3-5 years only if, on assessment, benefit persists.

WARNINGS AND ADVERSE EFFECTS (Contd)

Renal function should be routinely monitored in p with polyuria and polydypsia.

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 m Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremors, poly and mild thirst may persist.

Long term treatment with lithium is frequently associat with disturbances of thyroid function including goitre, hypothyroidism and thyrotoxicosis.

Mild cognitive impairment may occur during long term

Hypercalcaemia, hypermagnesaemia, hyperparathryoidism a an increase in antinuclear antibodies have also been reported.

Exacerbation of psoriasis may occur.

SIGNS OF IMPENDING TOXICITY

Appearance or aggravation of gastrointestinal symptoms, muscle weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitu blurred vision, coarse tremor, muscle twitching and a large output of dilute urine. At blood levels above 2-3 mmol/l, there is increasing disorientation, seizure coma and death.

PHARMACY

[redacted]

LEGAL STATUS

Lithium carbonate is available on prescription only ex where the maximum dose is the equivalent of 5 mg of th or less and the maximum daily dose is 15 mg of the base

RECOMMENDATION OF THE

COMMITTEE ON THE REVIEW OF MEDICINES

LITHIUM

INDICATIONS

Acute mania.

Prophylaxis of recurrent affective disorders.

DOSAGE

ACUTE MANIA

(As stated in the data sheets) - dose to be given in divided doses.

PROPHYLAXIS OF RECURRENT AFFECTIVE DISORDERS

600-1200 mg/day given in divided doses.
Clinical improvement is usually associated with serum concentrations of 0.5 mmol or above. Toxic symptoms are usually associated with concentrations exceeding 1.5 mmol.

USE IN ELDERLY

500-1000 mg/day given in divided doses.

Toxic symptoms are likely with serum concentrations above 1.0 mmol.

USE IN CHILDREN Not recommended.

MEASUREMENT OF SERUM LITHIUM CONCENTRATIONS

Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. On initiation of therapy serum concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals thereafter. Additional measurements should be made if signs of lithium toxicity occur (see below), on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs

As bioavailability varies from product to product (particularly with regard to retard or slow release preparations) a change of product should be regarded as initiation of new treatment. Blood levels should therefore be monitored weekly until re-stabilisation is achieved.

More frequent monitoring is required if patients are receiving diuretics.

CONTRAINDICATIONS

Renal disease

Cardiovascular disease

Addison's disease

Breast Feeding

USE IN PREGNANCY

There is epidemiological evidence that the drug may be harmful in human pregnancy. Should the use of lithium be unavoidable, close monitoring of serum concentrations should be made throughout the pregnancy and during parturition.

PRECAUTIONS

Pre-treatment and periodic routine clinical monitoring is essential. This should include assessment of renal function, urine analysis, assessment of thyroid function and cardiac function, especially in patients with cardiovascular disease.

Patients should be euthyroid before the initiation of lithium therapy.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Warnings and Adverse Effects). Patients should also be warned to report if polyuria or polydypsia develope. Episodes of nausea and vomiting or other conditions leading to salt/water depletion(including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Elderly patients are particularly liable to lithium toxicity.

DRUG INTERACTIONS

Lower doses of lithium may be needed during diuretic therapy as lithium clearance is reduced.

Raised plasma levels of ADH may occur during treatment.

Symptoms of nephrogenic diabetes are particularly prevalent in patients receiving concurrent treatment with tri/tetracyclic antidepressants.

Serum lithium concentrations may increase during concomitant therapy with indomethacin or tetracycline.

WARNINGS AND ADVERSE EFFECTS

Long-term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum clinically effective dose of lithium should always be used. Patients should be maintained on lithium after 3-5 years only if, on assessment, benefit persists.

WARNINGS AND ADVERSE EFFECTS (Contd)

Renal function should be routinely monitored in patients with polyuria and polydypsia.

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0 mmol.

Mild gastrointestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist.

Long term treatment with lithium is frequently associated with disturbances of thyroid function including goitre, hypothyroidism and thyrotoxicosis.

Mild cognitive impairment may occur during long term use.

Hypercalcaemia, hypermagnesaemia, hyperparathryoidism and an increase in antinuclear antibodies have also been reported.

Exacerbation of psoriasis may occur.

SIGNS OF IMPENDING TOXICITY

Appearance or aggravation of gastrointestinal symptoms, muscle weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle twitching and a large output of dilute urine. At blood levels above 2-3 mmol/l, there is increasing disorientation, seizures, coma and death.

PHARMACY

[redacted]

LEGAL STATUS

Lithium carbonate is available on prescription only, except where the maximum dose is the equivalent of 5 mg of the bas or less, and the maximum daily dose is 15 mg of the base or less.

~~0332/0015~~
0322/0015.

CRM 79/143

NOT FOR PUBLICATION

COMMITTEE ON THE REVIEW OF MEDICINES

RECOMMENDATION OF THE SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

LITHIUM

INDICATIONS

Acute mania

Prophylaxis of recurrent affective disorders.

DOSAGE

ACUTE MANIA

(As stated in the data sheets) -- dose to be given in divided doses.

PROPHYLAXIS

600–1200mg/day given in divided doses. Clinical improvement is usually associated with serum concentrations of 0.5mmol or above. Toxic symptoms are usually associated with concentrations exceeding 1.5mmd.

ELDERLY

500–1000mg/day given in divided doses. Toxic symptoms are likely with serum concentrations above 1.0mmol.

CHILDREN

Not recommended.

MEASUREMENT OF SERUM LITHIUM CONCENTRATIONS

Lithium therapy should not be initiated unless adequate facilities for routine monitoring of serum concentrations are available. On initiation of therapy serum concentrations should be measured weekly until stabilisation is achieved, then weekly for one month and at monthly intervals thereafter. Additional measurements should be made if signs of lithium toxicity occur (see below), on dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse and if significant change in sodium or fluid intake occurs.

Bioavailability varies from product to product including retard formulations. Serum concentrations should be measured as under "Measurement of Serum Lithium Concentrations" if a particular lithium preparation is changed for another.

DRUG INTERACTIONS

Lower doses of diuretics may be needed as diuretics reduce lithium clearance.

Symptoms of nephrogenic diabetes are particularly prevalent in patients receiving concurrent treatment with tri/tetracyclic antidepressants.

Serum lithium concentrations may increase during concomitant therapy with indomethacin or tetracycline.

WARNINGS AND ADVERSE EFFECTS

Long-term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High serum concentrations of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum clinically effective dose of lithium should always be used. Patients should be maintained on lithium after 3-5 years only if, on assessment, benefit persists.

Renal function should be routinely monitored in patients with polyuria and polydypsia.

Side effects are usually related to serum lithium concentrations and are infrequent at levels below 1.0mmol . Mild gastro-intestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremors, polyuria and mild thirst may persist.

Oedema and non-toxic goitre have occurred in some patients following prolonged treatment.

Exacerbation of psoriasis may occur.

More frequent monitoring is required if patients are receiving diuretics.

CONTRAINDICATIONS

Renal disease
Cardiovascular disease
Addison's disease
Breast feeding

USE IN PREGNANCY

Not to be used in pregnancy unless alternative therapies have proved unsuccessful, and the physician considers that the benefits outweigh the risks. Should lithium be administered, close monitoring of serum concentrations should be made throughout the pregnancy and during parturition.

PRECAUTIONS

Pre-treatment and periodic routine clinical monitoring is essential. This should include assessment of renal function, urine analysis, assessment of thyroid function and cardiac function, especially in patients with cardiovascular disease.

Patients should be euthyroid before the initiation of lithium therapy.

Clear instructions regarding the symptoms of impending toxicity should be given by the doctor to all patients receiving long-term lithium therapy (see Warnings and Adverse Effects). Patients should also be warned to report if polyuria or polydypsia develop. Episodes of nausea and vomiting or other conditions leading to salt/water depletion (including severe dieting) should also be reported. Patients should be advised to maintain their usual salt and fluid intake.

Elderly patients are particularly liable to lithium toxicity.

SIGNS OF IMPENDING TOXICITY

Appearance or aggravation of gastro-intestinal symptoms, muscle weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle twitching and a large output of dilute urine. At blood levels above 2-3 mmol/l, there is increasing disorientation, seizures, coma and death.

PHARMACY

1. [redacted]

[redacted]

LEGAL STATUS

Lithium carbonate is available on prescription only except where the maximum dose is the equivalent of 5 mg of the base or less and the maximum daily dose is 15 mg of the base or less.

NOT FOR PUBLICATION

COMMITTEE ON THE REVIEW OF MEDICINES

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

LITHIUM

1. Background

An ingredient report on lithium, together with suggested data sheet guideline recommendations, were seen by the Committee in October 1978 (Annex 1). At this time several reports of nephrotoxicity, including irreversible histological changes in the kidney, had just appeared in patients receiving long term lithium therapy (Annex 1, pp.7/8). The Committee, therefore, deferred their recommendations on the use of lithium in psychiatric disorders until results of known ongoing trials, which assessed renal function, were completed. Several further reports are now to hand and are summarized in this report.

2. New Data

i. Hestbech J et al. Lancet, Jan 27 1979, 212 (Annex 2)

Report possibly the first case of renal failure occurring in a patient following 3 years of lithium therapy. Blood levels (with one exception) had been maintained below 1.1 m mol. Renal function stabilised following withdrawal of lithium therapy. Renal biopsy showed focal interstitial cortical fibrosis and nephrotic atrophy.

ii. Hullin et al. BMJ, 2 June 1979, 1457-9 (Annex 3)

These authors investigated renal function in 106 patients attending a lithium clinic. They found the incidence of polyuria to be only 5.7% (compared with a 30% + incidence in previous reports) and a raised plasma creatinine was seen in approximately 5.5%. Creatinine clearance was reduced to below 50 ml/minute in approximately 15%. They suggested that the lower incidence of abnormal renal function in this series was due to the lower dose of lithium used. The average plasma lithium concentrations were maintained at 0.59 mmol/l (0.41 mg/100 ml) by a mean dose of 802 mg of lithium carbonate per day. In general, plasma levels are maintained at nearly twice this value. It is of significance that no increase in the relapse rate was observed by the present authors until plasma levels fell to below 0.4 mmol/l.

iii. B B Johnston et al. Brit J Psychiatry 134, 482, May 1979

Measured plasma and erythrocyte lithium concentrations in 49 manic depressives on routine lithium maintenance therapy. They found side effects in two-thirds (31) patients, which consisted mainly of tremors, or thirst, polydypsia-polyuria syndrome. Surprisingly, patients with side effects had significantly lower erythrocyte and plasma concentrations (0.394 and 0.787 mmol/l respectively than did those without side effects (levels = 0.56 and 0.93 mmol/l respectively). The erythrocyte/plasma ratio was 0.5 in the side effect group and 0.617 in the other.

iv. Other recent reports include:

a. A case of lithium poisoning which resulted in permanent neurologic, cardiac and hepatic damage following an intake of 2,700 mg/day for 10 days. Serum lithium reached 7.6 meg/l. Sequlae at 1 month following this episode of acute intoxication, included cerebellar and upper motor neurone symptoms, myocardial infarction and liver damage. (L H Warwick, The Western J. of Med. March 1979, 130, 3).

b. A report by J L Frolich et al (BMJ, 28 April 1979, 1115) showed a 59% increase in plasma lithium following concurrent medication with indomethacin, due to a reduction in lithium renal clearance (Annex 4).

c. A second report on the interaction of lithium and tetracycline (Annex 5) which describes a dramatic increase in serum lithium levels with signs of lithium toxicity 2-4 days after receiving tetracycline for a vaginal discharge.

v. A recent review on the renal toxicity of lithium published by the Drugs & Therapeutic Bulletin, V.17, 30 May 1979 (p.27/28) which also includes recommendations for use, is appended (Annex 6).

Medical Comment

The present state of knowledge regarding the effect of lithium on the kidney might be summarized as follows:-

Facts Established

a. Polyuria and polydypsia occurs in up to 40% of patients receiving long-term lithium therapy, probably due to antidiuretic hormone unresponsive diabetes insipidus.

b. Renal impairment/failure occurs in patients during acute lithium toxicity. Symptoms of failure including proteinuria, raised blood urea, oliguria etc. are usually reversible.

c. Permanent histological changes have been described in the kidney of patients following an episode of acute chronic lithium toxicity. In these patients, the impaired concentrating ability appears to correlate with the degree of histological involvement.

d. Histological changes have been observed (including "unique tubular lesion") in patients with no renal symptoms and normal renal function.

e. To date, the incidence of chronic renal failure - in patients receiving long-term lithium therapy is very low.

f. Plasma levels of lithium appear to relate, during chronic administration, to the symptoms of polyuria/polydypsia, and to the degree of renal failure and subsequent histological change, following acute intoxication.

Facts Unknown

a. The significance of the symptoms polyuria and polydypsia in terms of subsequent renal function and/or histological change, i.e. do they occur independently or are they the beginning of a process ending in nephrotoxicity/failure.

b. Relation between histological changes and impaired renal function.

c. Timescale involved if the common urinary symptoms and histological changes are associated with ultimate impaired function.

Although considerably more data is required before the exact role played by lithium in the pathogenesis of nephrotoxicity can be assessed, sufficient experience would now seem to have accumulated which will allow certain recommendations in this area to be made. Of particular interest is the association found by Hullin et al (Annex 3) between low serum lithium levels, and the low incidence of polyurea/polydypsia and raised plasma creatinine. Of equal interest is the fact that no increase in the incidence of relapse occurred until plasma levels fell below 0.4 mmol/l.
Although histological assessment was not made in this series, in view of the known functional and histological sequlae in the kidney following lithium intoxication, the maintenance of lowest effective plasma levels together with an adequate state of hydration would seem to be simple and rational measures recommend in an attempt to minimise renal damage.

Guidance with regard to the length of the treatment period, monitoring of renal, thyroid and cardiac function, and the desirability of starting long-term lithium therapy only in specific, well-defined conditions where lithium is of proven efficacy would also seem to be indicated.

Recommendations

The Committee are requested to approve guidelines for the use of lithium therapy.

[redacted]

September 1979

PRODUCTS ON THE UK MARKET CONTAINING LITHIUM CARBONATE

WITH INDICATIONS

	0108/0035 Phasal tabs 300 mg sustained release	0357/5000 Priadel tabs 400 mg sustained release	0332/0015, 5900 Camcolit 400, 250 tablets 400 mg, 200 mg.
1. Indications	1. treatment at acute manic or hypomanic episodes 2. prophylaxis against relapse in manic depressive disorders recurrent mania, or recurrent depression.	1. treatment of manic, hypomanic and depressive episodes 2. prophylaxis against relapse in recurrent mania, manic depressive illness and recurrent depression.	1. treatment and 2. prophylaxis of mania, manic depressive illness and recurrent depression.
2. Dose Acute mania	initially 600 mg bd increase by 300-600 mg /day if no response. Reduce dose once attack has subsided.	higher than normal doses necessary.	to be initiated in hospital 1500-2000 mg for 5 to 7 days, and adjusted after samples taken on 5th/7th day.
prophylaxis	600-1200 mg tabs/day in 1 or 2 doses, initially 600 mg in one dose.	1200-1600 mg as a single dose in morning or on retiring.	1000-1200 mg for 7 days, take a blood sample and adjust dose.
Children dose	not recommended		
3. Therapeutic blood levels	0.6 - 1.5 mEq/L do not exceed 2mEq/L.	0.6 - 1.5 mEq/L	0.6 - 1.2 mEq/L
4. Contraindication			
renal disease	significant renal disease.	severe renal disease.	in severe renal disease.
cardiovascular disease	significant cardoivascular disease.	severe cardiovascular disease.	
hypothyroidism	hypothyroidism	frank hypothyroidism	
Addison's disease		Addison's disease	
Sodium balance disorders	sodium depletion, or conditions requiring low sodium intake.		
5. Precautions			
pregnancy	not to be used in pregnancy unless alternative therapies have proved unsuccessful, and the physician considers that the benefits outweight the risk.	treatment to be discontinued as a general rule during planned or confirmed pregnancy - Li is secreted in breast milk. Babies may show signs of Li	contra-indicated in 1st trimester. Important to ensure adequate fluid and mineral intake in all hypothermic babies. Must be monitored

	PHASAL	PRIADEL	CAMCOLIT
	Blood levels to be monitored.	toxicity, and need fluid therapy as necates.	Li. Bottle feeding should be considered.
6. elderly patients	Use more cautiously as renal lithium clearance may be reduced.	recommended that starting dose is 800 mg (also if patient under 50 kg).	
7 Drug interactions			
diuretics	not to be used.	concurrent use contra-indicated.	lower doses of diuretics may be needed as diuretics reduce Li clearance. Frequent monitoring of patients essential
antidepressants	Li does not cause addiction or tolerance it maybe considered with the usual anti manic or antidepressive treatments.	all currently known antidepressant and anti manic drugs (including ECT) are compatible c priadel.	
diet	maintain a normal diet with adquate salt and fluid intake.	caution should be exercised to ensure that diet and fluid intake are normal, thus upholding a normal electrolyte balance.	

8 Side effects and warnings	0100/0035 Phasal tabs 300 mg S-R	0357/5000 Prindel tabs 400 mg S-R	0332/0015, 5900 Camcolit 400, 250 tabs 400 mg 250 mg
(i) pre-treatment examination	pre-treatment laboratory and physical examination is required, and should be repeated periodically	estimate serium Li levels to check whether patients are receiving Li in any other form. A creatinine clearance test should be performed if necessary	dinician to assess cardiac and renal function, including ECG if necessary. Lithium renal clearance test necessary
(ii) Frequency of blood sample monitoring :	measure blood levels weekly until stablized, and then weekly for the month after stabization, and then month monthly.	1st sample 4/5 days after starting treatment and weekly thereafter until stabilization acheived, estimations thereafter should not exceed 3 months.	determine weekly for 1st 3 weeks in acute mania. Li levels should be monitored at least 10 - weekly when stablizied.
(iii) Blood levels to be taken:-	(a) on changing Li preparations (b) on appearance of prodromel toxic signs, dosage alteration development of significant intercurrent disease, signs of manic or depressive relapse, change in Na or fluid intake, or during pregnancy and parturition.	when changing from other Li preparations. Daily dose to be as close as possible to other form of lithium. During pregnancy at signs of side-effects.	
maximum blood levels occur -	within 2-4 hours of dosing.		
(iv) Blood samples to be taken -		before daily dose.	12 hours after last dose.
Thyroid function		thyroid function tests approximately once yearly. Hypothyroidism can be treated with concurrent thyroxine.	thyroid function should be screened 3 monthly on prophylactic doses, as symptoms of depression are similar to those of early hypothyroidism. If one impair thyroid function concurrent thyroxine can be used.

	PHASAL	[illegible]	CAMCOLIT
adjust or reduce doses in cases of:-	early signs of toxicity.		sodium loss, impaired renal function as in exposure to extreme heat, vomiting, inter current infection, urinarytract infection or disease.
(v) stop treatment in case of:-	intoxication, such as appearance or aggravation of drowsiness, lethargy, coarse tremor, anoresia, vomiting and diarrhoea. (See also effects).	intercurrent renal infection; only to be re-instituted when kidney function is normal again also at signs of intoxication.	
transient side effect	infrequent below 1.5 mEq/L, mild g-i effects, nausea, vertigo, muscle weakness and a daze feeling.	unlikely below 2mEq/L fine hand tremor, mild polydipsia, mild polyuria, initial anorexia, some losening of stools more rarely nausea and diarrhoea.	nausea, loose stools, fine tremor, polyuria, and polypipsia.
persisent side-effects	fine hand tremor, polyuria mild thirst, oedema and non-toxic goitre have occurred after prolonged treatment.	weight gain and oedema may present in some patients.	find hand tremor, polyuria, and polydipsia weight gain and oedema may occur.
level of side effect and intoxication	aggravation of g-i effects, muscular weakness, lack of co-ordination, drowsiness, lethargy, increasing toxicity ataxia, giddiness, tinnitus blurred vision, coarse tremor, muscle hyper-irribility and polyuria. At 2-3 mEq/L increasing disorientation, coma and death.	increasing anorexia, vomiting and diarrhoea. Also mild drowsiness and sluggishness increasing to giddiness with ataxia, coarse tremor, tinnitus, blurred vision, muscular twitching, dysarthria progressing at 2-3 mEq/L to seizures coma and death.	vomiting, diarrheoa, coarse hand tremor, sluggishness, sleepiness, vertigo and dysarthria.

1. Background

1.1 Historical

Caelius Aurelionus first used mineral water with a probable high lithium content to treat mania in the 5th century AD. The element was discovered in 1817 by Arfvedson in Berzelius and various lithium salts were used during the 19th century in the treatment of gout and urinary calculi. In the early 1900s lithium bromide was used as an hypnotic and anti-epileptic, and later in the 1940s, lithium chloride was extensively used as a salt substitute. In 1949 there appeared the first report by Cade (Med. J. Aust. 2, 349, 1949) of the successful treatment of mania with lithium salts, but also in the same year, the first fatal case of lithium toxicity was reported where lithium had been used in place of salt. The toxicity associated with this use, together with the introduction of chlorpromazine in 1952 delayed the systematic use of lithium in psychiatry until the last decade. It was not until 1970 that the FDA licensed lithium for use in acute mania and in 1974 that use was extended to the prophylaxis of mania.

1.2 UK Products

There are four products with psychotropic indications currently marketed in the UK.

Priadel was first licensed in September 1968, followed by Phasal (Pharmax) in November 1973, Camcolit 250 mg (Norgine) in January 1976 and Camcolit 400 mg (originally but mistakenly thought to be a slow release preparation) in April 1977. Apart from bioavailability studies no original data on efficacy or safety has been submitted by companies. The data sheets for these preparations, together with a comparative summary of their contents, is appended.
Although licence indications are currently restricted to the treatment of mania and prophylaxis of bipolar affective disorders, a recent review of the literature (e.g, Lithium in Medical Practice, Ed. Johnson & Johnson, MTP 1978) shows at least 30 medical and psychiatric disorders where treatment involves the use of lithium.

2. Pharmacology

2.1 General

Lithium has the physical and chemical properties of other elements which belong to the first group of the periodic table, such as sodium and potassium. In general, lithium is more evenly distributed through body water than sodium or potassium, and so shows both extracellular features of sodium and intracellular features of potassium.
Like these elements, lithium has a high ionization potential and water solubility and so must influence a wide variety of physiochemical characteristics. These include pH, ionic strength, osmolarity and the biological properties of macromolecules. Theoretically therefore, lithium could influence the tertiary structure of macromolecules in cell membranes, hormone receptor sites, enzyme chains and chromosomes, and so control, directly or indirectly ionic selectivity of membranes, electrochemical gradients, responses to hormones, the coupling of energy processes to transport phenomena or even genetic expression.

2.2 Pharmacokinetics

Lithium salts are completely absorbed from the gastrointestinal tract - absorption being complete in 8 hours. Peak blood levels are reached in 0.5 - 2 hours, and plateau for 12-24 hours. Steady state plasma levels of 1.0 mg/kg are achieved in 5-6 days. Plasma half life is 18-24 hours. Lithium is not protein bound and distribution volume equals that of body water. Lithium crosses membranes slowly and enters tissues at varying rates. Peak concentration occurs in the kidney at 15 hours and in brain (rat) in 24 hours. Lithium is excreted entirely by the kidney, one-third to two-thirds of a single oral dose appearing within 6-12 hours. The remainder is excreted over 10-14 days. Discontinuation of lithium salts after chronic administration results in rapid renal excretion for the first 5-6 days, followed by slow elimination over a further 10-14 days.

2.3 Renal handling of lithium salts

The kidney handles lithium like sodium in the proximal tubule, where 60-70% of the filtered load is reabsorbed against electrical and concentration gradients. Lithium reabsorption in the distal tubules - unlike that of sodium is not quantitatively important and is insensitive to most diuretics which act distally. The effects of lithium on water flow are probably mediated through alterations in the ADH-sensitive adenylcyclase. In sodium depletion and dehydration, as might occur during diuretic therapy or in the elderly, increased lithium reabsorption occurs, so that toxic blood levels are rapidly reached, which are aggravated by the fall in total body water. This mechanism was also responsible for the toxicity seen when lithium salts were used in the place of sodium chloride.

2.4 Mechanism of Action

The exact mechanism of action is not known - indeed any of the pharmacological actions outlined above could, singly or in combination, contribute towards the therapeutic action of lithium. Recent hypotheses include changes in amine metabolism where ion substitution in critical areas could play a major role in the synthesis, storage release and/or re-uptake of noradrenaline and 5-hydroxy triptamine, changes in carbohydrate metabolism due to the insulin like action of lithium on glucose uptake and glycogen synthesis, or alterations in electrolyte and water distribution. Patients with mania responding to lithium have the largest increases in exchangeable sodium and sodium space, compared with non-responders or controls. This finding may be associated with the increase of sodium excretion found in mania in some studies. (In Jenner F A, Bioch. Soc. Spec. Publication 1, p.101, chapter 9, 1977). Lithium also increases plasma magnesium and increases Mg-ATPase in cell membranes. The relationship of those findings to each other, and to the therapeutic effects of lithium again is not known.

2.5 Long term biochemical effects of lithium therapy

These have been summarised by K Ghose (Brit. J. of Hosp. Med, December 1977, 578) in tables 1 and 2 overleaf.

Table 1. Important biochemical changes associated with long-term lithium therapy

Function	Effects of lithium therapy
Mineral metabolism	Summarized in Table 2
Monoamine metabolism	Increased 5HT synthesis Increased noradrenaline turnover
Carbohydrate metabolism	Insulin released Increased muscle glycogen
Cyclic AMP	Inhibited
Thyroid function	Decreased synthesis of thyroid hormones
Renal function	Increased aldosterone secretion initiall Distal renal tubule becomes relatively insensitive to antidiuretic hormone Probable increase in antidiuretic hormone

Table 2. Effect of lithium on mineral metabolism (data from Christiansen et al, 1976)

Mineral	Effect of lithium therapy
Sodium	Reduced concentration in central nervous system
Potassium	No significant change
Magnesium	Increased concentration in muscle and serum Decreased uptake in bone
Calcium	Increased concentration in serum Decreased uptake in bone
Phosphate	Increased uptake in muscle and liver Decreased uptake in bone
Bone mineral content	Reduced
Parathormone	Slightly increased (subclinical)

2.6 Other pharmacological effects of lithium include the potentiation of ethanol-induced sleeping time (Messiha F S, Pharmacology, 1976, 14, 153), potentiation of neuromuscular blockade by muscle relaxants (Hill et al, Anaesthesia 1977, 46, 122) and the action of pentobarbitone in mice (Diamond et al, Lancet, December 10, 1977). Several recent reports have also shown lithium to produce agranulocytosis, which effect is currently under trial in patients with drug induced granulopenia (Glenn Tisman, Lancet, July 30, 1977). Some immuno-stimulating activity has also been demonstrated by Shenkman et al (Clin. Res. 1976, 27, 654) who found increases in lymphocyte transformation and macrophase phagocytosis in lithium fed mice.

2.7 Blood levels and dosage

i. Unlike many psychotropic drugs, the administered dose of lithium bears a direct relationship to blood levels, and blood levels to clinical efficacy and toxic effects.

ii. Initially the therapeutic blood level range was considered to be 0.6 - 1.6 meq/l (as in Martindale 28th Ed) but most investigators feel 1.6 meq/l is in the toxic range. Salkind (J. Royal Col. Gen. Pract, 20, 13, 1970) suggested a range of 0.6 - 1.5 meq/l, and Schou (Br. J. Psychiatr. 116, 615, 1970) and Bennie et al (Lithium in Med. Practice, 1978, p.381, ed. Johnson & Johnson, MT Press) thought the most suitable range to be 0.7 - 1.2 meq/l. When the patient is standardised, a dosage of 600 mg - 1600 mg will usually achieve these levels. As the therapeutic range is narrow, regular monitoring is essential, particularly during the initial stabilization period. Blood levels should be sampled at the same time after each dose.

iii. Toxic symptoms (see below) occur with blood levels of 1.6 - 3.0 mmol/l with death occurring with levels from 3.0 - 4.0 mmol/l.

iv. Although lithium has a long half life and theoretically could be given once per 24 hours, the highest blood level peak falls within the toxic range and BD administration is advisable. Recent studies have shown sustained release preparations are as effective as ordinary preparations, and compared with BD administration, are less likely to reach toxic levels.

3. Toxicity

3.1 Adverse Reactions

The side effects of lithium therapy fall into three general areas - those usually minor symptoms occurring when blood lithium levels are within the normal therapeutic range, those serious symptoms occurring with high blood lithium levels i.e, lithium toxicity, and adverse reactions occurring with chronic lithium administration.

i. Early side effects

Minor side effects are common, especially when first starting therapy. These include nausea, intestinal upsets, thirst, polyuria, skin rashes and tremors, and occur even though blood levels are within the therapeutic range. These effects may lessen following dose stabilization.

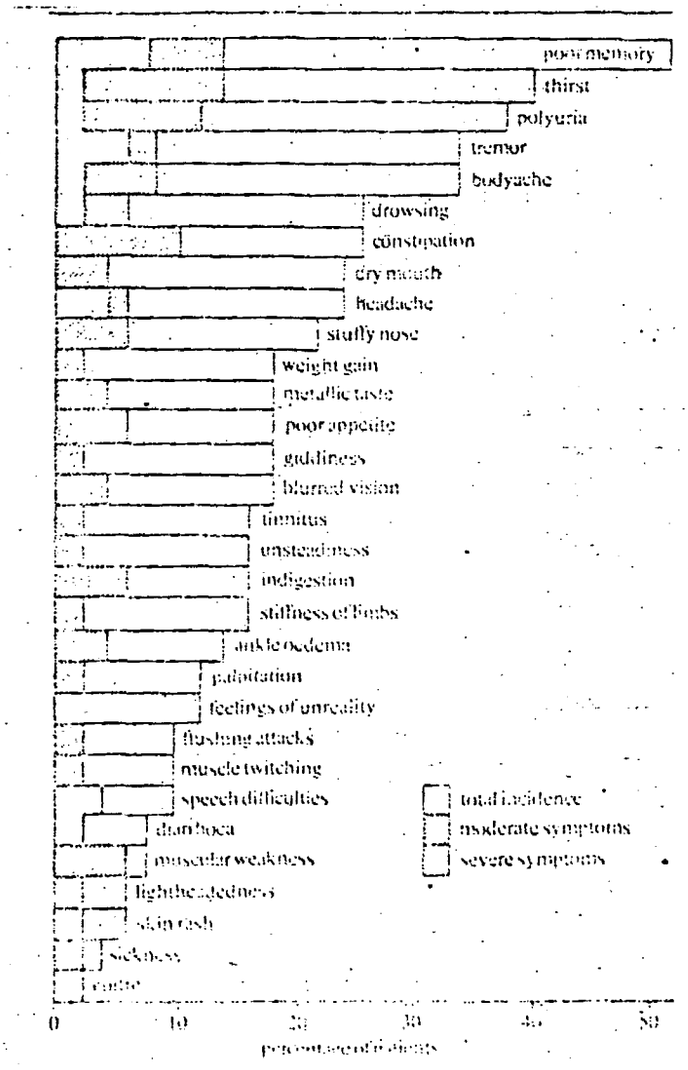
ii. Lithium toxicity

In general, the occurrence and severity of lithium toxicity is directly proportional to lithium blood levels. Normal therapeutic blood levels of 0.6 - 1.5 mmol/l can be associated with lithium toxicity in the elderly, in patients with pre-existing brain damage, in schizophrenia, and in association with some drugs given concomitantly with lithium (see below).

In most patients symptoms of toxicity occur with blood levels approaching 2.0 mmol/l. These include blurred vision, tremor, ataxia, diarrhoea and dysarthria and patients should be warned of the significance of such symptoms. Blood levels of 2-4 mmol/l lead to disorientation, cardiac arrhythmias, muscle hyperactivity, convulsions, coma and death, or irreversible brain damage. Dehydration and sodium depletion from any cause result in lithium retention and raised plasma levels leading inevitably to severe toxicity. Most diuretics (see below) are particularly dangerous in this respect, and a recent case of lithium toxicity has been reported following dieting and saunas (Tonks, BMJ, 26 November 1977, p.1596). Treatment of lithium toxicity includes sodium and fluid replacement and peritoneal dialysis.

iii. Long term treatment

Common symptoms occurring during long term treatment, include polyuria, polydypsia, fine finger tremor, weight gain and hypothyroidism. The pathological effects on the kidney, thyroid and heart are the most serious to occur and will be considered in more detail below. The incidence of subjective symptoms in patients receiving lithium therapy at the MRC Neuropsychiatry Laboratory have been reported by K Ghose in B. J. of Hosp. Med. December 1957, 578, and are reproduced below.



iv. Other

Three cases of diabetes mellitus have recently been reported following long term lithium therapy (Craig et al, Lancet, November 12, 1028, 1977; B B Johnston, Lancet, October 29, 935, 1977).
Two cases of lithium induced nephrogenic diabetes have also been reported by Price et al (Ann. Int. Med 88, 536, April 1978) where blood lithium levels were within the therapeutic range.

The Swedish Adverse Drug Reaction Committee (Notice 26, May 1977) have described 9 cases of exacerbation of psoriasis where patients were treated with lithium. The causal relationship between lithium and psoriasis was established by the time course on introducing and withdrawing the drug. As lithium is known to inhibit adenylcyclase activity, and the content of cyclic AMP in psoriatic skin is reduced, it is thought that lithium may elicit or worsen psoriasis by interfering with this system.

3.2 Lithium and the kidney

The major target of lithium toxicity to emerge over the last decade is the kidney. Although polyuria and polydypsia have been known to occur frequently during lithium treatment, and early animal studies by Schou showed the kidney to be a target organ of toxicity in animals, the occurrence of these symptoms have not been thought indicative of serious or progressively deteriorating renal function. Recent studies over the past year or so, however, have shown that irreversible histological changes can occur in association with normal therapeutic blood levels of lithium. This finding, in the opinion of some investigators, could lead to a reconsideration of the criteria used for long term lithium use. As there is current interest and controversy regarding the relevance of lithium produced changes and the kidney, this topic is discussed in some detail.

Animal Studies

i. In 1958, Schou found high doses of lithium given to rats produced oliguria, azotemia, lithium retention and irreversible renal tubular damage. A high sodium diet gave some protection (Acta Pharmacol. Toxicol 15, 70, 1958).

ii. Evan in 1972 (Evan & Ollerich, Am. J. Anat. 134, 97, 1972) showed lithium carbonate given in therapeutic doses (10-30 mg/kg) in cats and dogs gave ultramicroscopic mitochrondrial damage in the distal hephron. The reversibility of the lesion was not determined.

Human studies

i. Acute changes during lithium toxicity

A number of authors including Schou et al (J. Psych. Res. 6, 67, 1968) have found raised blood urea, serum creatanine and oliguria in patients with lithium toxicity. These symptoms are usually reversible.

ii. Diabetes Insipidus

Chronic lithium administration is known to impair concentrating and acidifying abilities in man and animals (Bucht & Wahlin, Lancet April 8, 1978, p.778). At least one-third of lithium treated patients have ADH unresponsive diabetes insipidus. Some 55 articles on lithium induced polyuria and polydypsia have now appeared, giving the incidence of some degree of diabetes insipidus as over 40%. In most patients the symptoms seem mild and well tolerated. The possible mode of action of lithium is thought to be associated with the inhibition of ADH-sensitive renal adenylcyclase. Lithium significantly inhibits ADH induced water transport in the toad bladder but does not affect c AMP-induced water flow. A possible central action of lithium on ADH synthesis/storage/release mechanisms might also be involved.

iii. Histological Changes.

a. Hestbech et al (Kidney Int. 1977, v.12, p.205) published one of the first studies showing histological kidney changes in human patients. In 13 out of 14 patients with acute lithium intoxication, he found focal nephron atrophy and/or interstitial fibrosis. Sclerotic glomeruli were five times as common in patients on lithium compared with age matched controls, tubular atrophy three times as common and lithium patients had twice as much connective tissue. These patients showed proteinuria only during the period of acute intoxication - otherwise no significant findings referable to the kidney function were seen.
In a second study by the same authors involving 13 (8 from the above series) with structural kidney changes, only osmolar concentrating deficiencies were seen.

b. Burrows, Davies & P. Kincaid-Smith (Lancet, 17 June 1978, p.1310) in a letter to the editor, reported histological kidney lesions in 5 patients who had received lithium therapy for 4 months to 9 years. They described a "unique tubular lesion" in the distal convoluted and collecting tubules, which included PAS positive granular material in the wall of cells radiating from the nuclei and large intense staining in the cytoplasm of cells before other damage was visible. Amorphous PAS positive casts were also prominent, as well as ballooning and vacuolation of cells and cytoplasm. Only minor changes were observed in the proximal tubules. Changes were more advanced the longer the patient had received lithium - some 20% of glomeruli were seen to be sclerosed with tubular atrophy and interstitial fibrosis.
Renal function in these patients was normal and urine contained neither protein or excess RBCs i.e, the usual indications for renal biopsy were absent. Because of the apparent progressive nature of the lesion, in spite of normal function, these authors considered that long term lithium treatment should be reserved for the treatment of bipolar affective disorders only and, that tricyclics should be used in patients with recurring depression, in the absence of cardiac problems.

c. Inpharma (13 May 1978, p.6) note that 3 further cases of impaired kidney function and biopsy confirmed renal pathology had been reported at the Scandinavian Soc. of Psychopharmacology. The figures reported suggested a 15-20% incidence of renal pathology in lithium treated patients. However they also considered terminal azoteamia unlikely to develop and that most risk from the kidney was likely to be due to a decreased urine concentrating ability leading to dehydration, and an increased risk of lithium toxicity.

d. Schou & Jenner (Lithium in Medical Practice, MTP 1978) have both suggested that life long lithium therapy must be weighed against not only the histological lesions but functional abnormalities of the kidney and the quality of life which may be lithium dependent. Both investigators feel that renal insufficiency is uncommon in long term lithium patients and that if only the capacity to concentrate urine appears to be impaired, life need not be endangered.

3.3 Lithium and cardiovascular effects

Adverse effects of the heart, including reversible flattening or inversion of T waves and arrhythmias have been reported (Jaffe, Am. J. Psych. 1977, 134, 88; Demess et al, Dis. of Nerv. Syst. 1970, 31) and the safety of long term lithium therapy in patients with cardiovascular disorders has been questioned. In a recent review of the cardiovascular effects of lithium in man, however, Tilkian et al (Am. J. of Med. 1976, 61 (5), 665) has shown significant CVS effects such as hypotension and "cardiovascular collapse" occur only in severe lithium toxicity. On normal therapeutic doses T wave flattening and, rarely, sinus node dysfunction and ventricular arrhythmias can occur, but are reversible. He concludes that lithium is safe to use if dose is adjusted to rate of lithium excretion with close monitoring of serum levels.
In patients with cardiac arrhythmias Tilkian advises frequent ECG monitoring and points out that patients with congestive cardiac failure or on salt restriction are particularly liable to lithium toxicity.
In experimental animals, lithium produces hypercalcaemia and hypermagnesaemia with associated ECG changes.

3.4 Lithium and the thyroid

Schou first reported in 1968 (BMJ, 1968, 3, 710) the occurrence of hypothyroidism in patients taking lithium carbonate or sulphate. The incidence of thyroid deficiency is now considered to be 5-15% (Lindstedt et al, Br. J. Psych. 1977, 130, 452: Lazarus and Bennie, Acta Endocrinologia 1972, 70, 260).
Two cases of irreversible myxoedema, without goitre, have recently been reported (Persild et al, BMJ, 1108, 29 Apr. 1978)
Goitre can also occur, with or without symptoms of hypothyroidism.
Lithium appears to inhibit the release of iodine T_3 and T_4, from the thyroid gland so that decreased circulatory levels peripherally, stimulate TSH production resulting in thyroid enlargement.

Berens & Wolff (Lithium Research and Therapy, ed. Johnson, Ac. Press, 1975, p.445) reported that out of 350 patients developing goitre over 5-24 months of lithium therapy, none were clinically hypothyroid and the overall incidence of goitre was 4%. In other series however, up to 20% of patients with goitre have been clinically hypothyroid. Lithium may also produce abnormal laboratory tests in the presence of clinical euthyroidism. Christiansen et al (Neuropsychobiology, 1975, 1-344) has reported that hypothyroidism is more likely in woman and may be accompanied by raised serum calcium and magnesium concentrations. Perez et al (Clin Pharm. & Therap. 1977, 21, 449) has suggested that these changes may be due to direct action of lithium on the parathyroid glands. Lithium induced thyrotoxicosis has also been reported (Franklin, New Zealand M. J. 1974, 79, 782).

3.5 Drug Interactions

i. Introduction

In general the use of lithium with other drugs is fairly well tolerated. The most serious consequences are seen with diuretics and possibly with some neuroleptics, such as haloperidol. These are discuss in some detail below. Lithium apparently does not adversely interact with the tricyclic antidepressants, and may even act synergistically (Lingjaerde et al, Acta Psychiatr. Scand. 50, 233, 1974).
No adverse reactions have been reported with either the MAOIs or orally administered anxiolytics, although a recent report has appeared of hypothermia occurring when iv diazepam was used in a patient on lithium therapy (Murphy, BMJ, 2 July 1977, 642).

ii. Lithium and diuretics

The excretion of lithium is closely linked with that of sodium in the kidney and most clinically used diuretics on a long term basis can be expected to cause lithium retention, high serum levels with a corresponding higher risk of lithium toxicity. The mechanism is thought to be due to both reduced renal clearance of lithium with thiazides - which Penst et al found to be 26% in normal volunteers (Psychopharmacol. Commun. 2, 273, 1976) and reduction in total body water and sodium by action of the diuretic. Salt restriction and dehydration exacerbate the high risk of severe toxicity.

iii. Lithium and haloperidol

Toxic neurological symptoms including rigidity, ataxia, and tardive oral dyskinesia, have been reported by Cohen & Cohen (JAMA, 230, 1283, 1974); Mashold et al (Act. Nerv. S[illegible] 16, 199, 1974) and London and Wering (Lancet ii 1088, 1976), when lithium is used in combination with haloperidol. These authors suggest that neurotoxicity including irreversible brain damage can occur when haloperidol is used in doses of over 40 mg/day when blood lithium levels are maintained at 1 mmol/l or over. However, Baastrup et al (JAMA 236, 2645, 1976) reviewed 425 hospital patients treated simultaneously with both lithium and haloperidol and found the incidence of adverse reactions the same as in patients treated with either drug alone. These authors, on reviewing Cohen & Cohen's cases found, because of the mixed drug history, a direct relationship between a combined lithium and haloperidol therapy and neuro-toxicity difficult to establish.

iv. Miscellaneous drug interactions

a. Chlorpromazine. A study by Kerzner et al (Clin. Pharmacol. Ther. 19, 109, 1976) suggests that concurrent administration of chlorpromazine with lithium may depress lithium blood levels due to delayed stomach emptying.

b. Methyldopa. Methyl-dopa may increase lithium toxicity even though blood levels are within the therapeutic range. Two cases have so far been reported.

c. Anticonvulsants. Speirs & Hirsch (in Lithium in Medical Practice, MTP 1978) report lithium toxicity with normal blood levels in a patient concomitantly receiving phenytoin and phenobarbitone. Serum lithium decreased following initial stabilization, and doubling the dose to 2000mg/day produced blood levels of 0.8 mmol/l. Toxic symptoms included diarrhoea, tremor and coma. The patient recovered after complete lithium withdrawal.

d. Neuromuscular Blocking Agents. Two reports are also available which suggest that lithium may prolong the action of the nondepolarising neuromuscular blocking agents - pancuronium bromide and succinyl chloline. This action of lithium has been confirmed in animals (Reimherr et al, Am. J. Psychiat. 134, 205, 1977).

4. Teratology

4.1 Animals

High doses of lithium in animals show in general an increased tendency towards impaired fertility and malformations in the offspring, particularly with parenteral preparations and high single daily doses. Graffa & McIlpenny however, found no abnormalities in rats when lithium was given in divided doses at therapeutic levels (Pharmacol. 21, 428, 1972).

4.2 Humans

Since 1968 a Scandinavia register has been kept for babies born to mothers receiving lithium. A similar register is kept in California.

In 1977, 166 babies had been born to mothers who had received lithium carbonate during the first trimester of pregnancy. Of these 18 had malformations, the greatest number involving the heart and major blood vessels. Nora et al (Lancet 2, 594, 1974) reporting on 13 lithium babies showed 10 to have abnormalities involving the heart and great vessels (4 having Ebsterin's malformation of the tricuspid valve) and 1 an abnormality involving the umbilical artery.

A follow-up at 5 yrs of 60 of the normal babies born to lithium mothers on the Scandinavian register showed no significant difference with regard to developmental abnormalities between these and controls.

4.3 Chromosome Studies

Friedrich & Nielsen found chromosomal abnormalities in in-vitro studies with human leukocyte chromosomes at concentrations of 2-4 mg/1 - (Lancet 2, 435, 1969).
Ten chromosome breaks in seven out of eight infant leukocytes were also seen in a baby with multiple deformities born to a mother with acute lithium toxicity during pregnancy (CMA, Oct 23, 1971, 105). However, Weinstein & Poldfield (Am. J. Psych. 132, 529, 1975) found that lithium at therapeutic concentrations had no significant effect on chromosomes in man.

4.4 Lithium intoxication in the newborn

Hypotonic, floppy listless babies have been reported to have been born to lithium toxic and non-toxic mothers. The babies usually recover without special treatment (Woody et al, Paediatrics 47, 94, 1971). Two cases of tyroid abnormality have been reported in the newborn.

4.5 Breast Feeding

Lithium passes into breast milk at half the plasma concentration.

5. Therapeutic Efficacy

5.1 Treatment of acute mania

Following Cades original observation in 1949, lithium after a slow start, has now become the treatment of choice for mania and hypomania. In 1968

Schou reviewed 32 publications (J. Psychiat. Res. 6, 67, 1968) of which 31 demonstrated the therapeutic efficacy of lithium in acute mania. Numerous more recent studies have confirmed that lithium can be expected to control the symptoms in acute manic patients in 70-80% of cases (ref. in Lithium Research & Therapy p.25, ed. F N Johnston, Ac. Press 1975).
Relapse following withdrawal of treatment was demonstrated by Burney et al (Am. J. Psychiat. 125, 499, 1968) and the therapeutic superiority of lithium to chlorpromazine in the highly disturbed acutely manic has been shown by Warton & Fiene (Am. J. Psych. 123, 706, 1966) and Takahashi et al (Arch. G. Psych. 32, 1310, 1975).

In gneral, the effect of lithium is seen 5-10 days after starting therapy, but maximum effectiveness may not be seen for some weeks or even months. It appears to benefit mostly patients with the pure elation, hyperactivity, pressure of speech syndrome rather than patients with delusions and hallucinations.

5.2 Prophylaxis of mania and bipolar affective disorders

i. Recurrent Mania

Early studies which suggested that lithiumwas effective in preventing as well as treating recurrent attacks of acute mania, were criticized in 1968 by Blackwell & Shepherd (Lancet, May 4 1968, 968) as being mainly open trials which failed to establish efficacy in the prophylaxis of mania. In 1970, Baaskrup et al (Lancet, ii, 326) carried out a double blind, randomised trial where placebo or lithium was given to patients already receiving lithium. The relapse rate was strikingly different between the two groups. Subsequent experience has confirmed the efficacy of lithium in the prophylaxis of recurrent mania and hypomanic states (Lithium in Medical Practice, MTP, 1978).

ii. Bipolar affective disorders

a. The efficacy of lithium in prophylaxis of the recurrent depressive pole of the illness has taken longer to establish. However, the conclusion in 1975 of the American Psychiatric Association task force on lithium therapy (reported in Primer of Lithium Therapy, J W Jefferson and J M Preis, Williams & Wilkins 1977, p.18) was that "lithium is effective in the prophylaxis of bipolar affective illness with regard to both the manic and depressive symptoms". Efficacy of lithium in an illness which is mainly depressive is less well established, although the above task force also concluded that there was "persuasive evidence from controlled studies that (lithium) is also effective in the prophylaxis of unipolar depressive illness". They warned of the necessity of exactness in definition of unipolar illness and the need for further trials.

b. Anath et al (J. Clin. Psychiatry 39, 95, 1978) have recently reviewed the use of lithium in recurrent depression, and has emphasized the relationship of precise diagnosis to a high incidence of "good responders". These authors suggested that a good therapeutic effect could be predicted in 80-90% of patients with depressive symptoms if (1) a definite diagnosis of primary affective disorder had been made,
(2) less than 4 episodes of mania and depression occurred per year,
(3) psychotic features were present during manic and depressive episodes (e.g. grandiose, elated, during mania etc) and that
(4) there was a family history of bipolar illness with response to lithium by affected members.

The search of identification of "good responders" has shown some biochemical differences between those responding to lithium therapy.
Flennenbaum et al (Am. J. Psychiat. 336, Mar. 1978) found a higher red blood cell/plasma lithium ration (0.41) in a study of 33 depressive unipolar 'responders' after 17 months of lithium therapy which als included schizo-affective psychoses and alcoholics. Sullivan et al (Lancet, Dec. 1977, 1325) showed that platelet MAO activity of resonders in manic depressive psychosis similar to that of normal controls whereas that of non-responders was less.

Although some authors feel that the role of lithium with regard to recurrent depressive symptoms is not fully defined and that patients with bipolar illness are more likely to respond than those with recurrent unipolar depression (e.g, Threndels 1976, reviewed 9 uncontrolled and 10 uncontrolled trials showed statistically significant results in only 3 of the ten controlled trials), Schou has recently stated (Lithium in Medical Practice, p.21 ed. F N & S Johnson, MTP, 1978) that "efficacy (of lithium) in prophylaxis in recurrent affective disorders is now well established. Lithium will either attenuate or prevent depression in monopolar as well as bipolar disorders". Lithium is not approved by the FDA however, for either the prophylaxis or treatment of unipolar depression.

5.3 Treatment of Acute Depression

E H Bennie has recently summarised the results of 14 clinical studies where lithium has been used in the treatment of acute depression (Lithium in Medical Practice, MTP 1978). The results are summarised below:-

Type of Study	Uncontrolled Studies	Controlled Studies
Number of patients	189	128
Number responding to Lithium	110	51 (77)*
% improvement	52	40 (60)*
Number of studies	9	5

* Partial response.

It is evident from these results that tricyclic antidepressants or ECT are considerably more effective in the treatment of acute depressive illness. The task force of the American Psychiatric Assocn (1975) concluded that "experimental results are not sufficiently conclusive to permit a clear definition of the value of lithium in acute depression".

6. Medical Comment

Over the past 10-15 years, lithium has become established as the treatment of choice in acute mania and in the prophylaxis of recurrent bipolar affective disorders. Although the exact mechanism of action is unknown, it appears to have a specific, rather than general, effect in patients with recurrent mania. This point is illustrated by relatives observing that the patients "appear their normal selves and not drugged" when responding to lithium therapy (Jenner in Lithium in General Practice, MTP 1978).

In recurrent affective disorders where depressive symptoms predominate, efficacy of lithium is less well established. Successful treatment in these patients may depend upon the recognition by meticulous history taking, strict diagnostic criteria, and possibly biochemical means of a specific subgroup of "lithium responders". Lithium appears to be of little benefit in the treatment of acute depressive illness.

In general, lithium is well tolerated and, with the exception of diuretics and possibly some neuroleptics, can be administered concurrently with other drugs with relatively few untoward effects.
The major acute problem is lithium toxicity - which occurs when blood levels exceed 1.6 mmol/l and is precipitated and accelerated by dehydration, salt restriction and diuretics.
Adequate instructions to patients regarding the circumstances and symptoms of impending toxicity have been found to minimise this problem. Particular care in monitoring should also be taken of patients with cardiovascular disease.

The major side effect of chronic lithium treatment - and the one which is of current concern, is the problem of irreversible kidney damage. Although histological changes have been found in the kidney following months to years of therapy (and in the absence of lithium toxicity) the relationship of these changes to function - other than impairment of concentration and acidifying ability is not known. In the absence, so far, of reports on chronic renal failure occurring, most investigators feel that as long as strict diagnostic criteria are observed in prescribing long term lithium therapy the risks are justified by the improvement in the quality of life experienced by patients responding to lithium (see recent reports on Lithium and Kidney, appended, Annex 3).
Early detection by regular monitoring of both renal (including urine for sugar) and thyroid function might prevent the development of severe progressive lesions occurring in the tissues.
Theoretically, lithium with its long half life, could be administered in a single daily dose. Reports have shown, however, that even with sustained release preparations, blood levels peak in the toxic range so that BD administration would seem desirable. There would seem to be relatively little difference between the available preparations, particularly as therapeutic blood levels are maintained by biochemical control.

Although 95-98% of babies born to mothers receiving lithium are normal, lithium has been shown to cause teratogenic abnormalities, particularly of the heart and great vessel, so that this risk must be weighed against any therapeutic benefit.

7. Recommendations

The Committee might consider the following modifications or additions to be made to the data sheets of lithium products:-

1. Indications — Treatment of acute mania - Prophylaxsis of recurrent bipolar affective disorders (Acute and recurrent depression omitted).

2. Dose levels — As stated - but twice daily.
Children. Not recommended.

3. Therapeutic Blood Levels — 0.6 - 1.2 meq/l/mmol/l

4. Contraindications — As for Phasal - plus Addison's disease.
Add - excessive use of diuretics; breast feeding.

(P) 5. Pregnancy — As stated.

(P) 6. Elderly patients — Include warning.

(W.A.E.) 7. Drug Interactions

Diuretics - as stated.
Antidepressants - as stated.
Diet - as for Priadel.

Add warning regarding possible interaction with Haloperidol and any drugs which may lead to dehydration or salt depletion

8. Side effects and warnings

(P) (i) Pre-treatment and periodic routine monitoring. — assessment of renal function, serum electrolytes; cardiac function with ECG if indicated. Thyroid function. Urine for sugar. Add close monitoring is essential if diuretics necessary or in patients with cardiac disease.

(W) (ii) Frequency of blood monitoring and (iii) blood levels to be taken — As for phasal. Add exposure to extreme heat, intercurrent infection, urinary tract infection or disease, as in Camcolit.

(W) (iv) Time — Take blood sample (same time after each dose).

(W) (v) Stop treatment in case of — as for phasal and priadel. Add clear instruction to doctor to inform patients of symptoms of impending toxicity. Add Warning regarding delay in therapeutic action.

(SE) SIDE EFFECTS

(SE) Transient side effects - infrequent below 1.5 meq/l, other as stated

(SE) Persistent side effects - as stated.

Level of side effects and intoxication - as stated - see warning 8 (vi) above.

Add (a) warning re worsening of psoriasis.

(b) possible long term effects on kidney.

(c) diabetes.

PHASAL

Pharmax Ltd

PHASAL®

Presentation White tablets of diameter 0.5 inch, marked on one side with 'P' inside a hexagon. Each Phasal contains 300 mg Lithium Carbonate BP in a sustained release presentation.

Uses Lithium is an antimanic agent; it can also exert a stabilising influence on recurrent affective disorders. Recommended uses:

1. Treatment of acute manic or hypomanic episodes.
2. Prophylaxis in manic-depressive disorders, recurrent mania or recurrent depression.

Dosage and administration Dosage must be adjusted in the individual patient, according to clinical condition and the results of regular blood lithium determinations.

1. *Acute episode:* Initially 2 tablets b.d. Increase by 1 or 2 tablets per day if no response. Maintain blood lithium levels in optimum range 0.6–1.5 mEq/l; do not exceed 2 mEq/l. Dosage should be reduced rapidly once the acute attack subsides.

2. *Prophylaxis:* Usually 2–4 tablets per day administered in 1 or 2 doses. Maintain blood lithium levels in range 0.6–1.5 mEq/l.

When starting directly on prophylactic therapy administer 2 tablets in a single dose initially, with subsequent increments of 1 tablet until adequate blood levels are achieved. When changing from an alternative lithium preparation administer the same daily dosage initially and modify if necessary according to blood-level determinations.

Blood-level monitoring: Blood levels should be determined by taking a blood sample before the daily dose. Initially this should be done four to five days after commencing Phasal treatment. Weekly checks are recommended for the month following stabilisation, and then monthly determinations may suffice. With lithium preparations maximum blood levels normally occur within two to four hours of dosing. Blood levels should also be determined on the following occasions: appearance of prodromal toxic signs, dosage alteration, development of significant intercurrent disease, signs of manic or depressive relapse, significant change in sodium or fluid intake, or during pregnancy and parturition.

Phasal does not cause addiction or tolerance. It can be safely combined with the usual antimanic or antidepressive treatments.

Tablets must be swallowed whole.

Contra-indications, warnings, etc

Contra-indications: Significant renal or cardiovascular disease, hypothyroidism, sodium depletion, or conditions requiring low sodium intake.

Precautions: Pre-treatment laboratory and physical examination is required, and should be repeated periodically.

The patient should be advised to maintain a normal diet with adequate salt and fluid intake. Diuretics should not be used during lithium therapy.

Lithium intoxication seldom occurs suddenly. The patient must be instructed to discontinue therapy and report to the doctor should prodromal toxic signs occur, such as appearance or aggravation of drowsiness, lethargy, coarse tremor, anorexia, vomiting or diarrhoea (see also Adverse effects).

Phasal should not be used in pregnancy or women of child-bearing potential unless alternative therapies have proved unsuccessful and the physician considers the potential benefits outweigh the possible hazards.

Phasal should be used more cautiously in the elderly, in whom renal lithium clearance may be reduced.

Phasal is not recommended for use in children.

Adverse effects: Side-effects are usually related to blood lithium levels, and are infrequent at levels below 1.5 mEq/l. Mild gastro-intestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremor, polyuria and mild thirst may persist. Oedema and non-toxic goitre have occurred in some patients following prolonged treatment.

Appearance or aggravation of gastro-intestinal effects, muscular weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle hyperirritability and a large output of dilute urine. At blood levels above 2–3 mEq/l, there is increasing disorientation, seizures, coma and death.

Overdosage: Early signs of toxicity usually respond to reduction or cessation of dosage.

There is no specific antidote for lithium poisoning. Treatment comprises general supportive measures and maintenance of electrolyte balance. Elimination of lithium may be facilitated by infusion of sodium bicarbonate, acetazolamide, urea or mannitol.

Prolonged continuous peritoneal dialysis may be more effective than haemodialysis.

Pharmaceutical precautions Store in a cool dry place.

Legal category POM.

Package quantities Securitainers of 100 and 500 tablets.

Further information Phasal is a sustained release preparation designed to facilitate control of blood lithium levels within the optimum range. The smaller diurnal variation produced by the once or twice daily dosage regimen: i) reduces the risk of rapid and excessive absorption of lithium and thereby improves safety; ii) maintains the desired blood levels and so provides continuous protection against relapse; iii) improves convenience of dosing for the patient.

Product licence number 0108/0035.

PRIADEL®

Presentation Controlled release lithium carbonate tablets: white circular, scored bi-convex tablets engraved PRIADEL one side. Each tablet contains 400 mg Lithium Carbonate BP in a controlled release dosage form.

Uses Controlled release lithium therapy for:

a) The treatment of manic, hypomanic and depressive episodes of recurrent affective disorders.

b) Prophylaxis against relapse in recurrent mania, manic depressive illness and depressions.

Dosage and administration A simple treatment schedule has been evolved, which, except for some minor variations, should be followed whether using PRIADEL therapeutically or prophylactically. The minor variations to this schedule depend on the elements of the illness being treated and these are described later.

1. In patients of average weight (70 kg), 3–4 tablets (1,200–1,600 mg) of PRIADEL are given as a single daily dose in the morning or on retiring. In elderly patients or those below 50 kg, it is recommended that the starting dose be reduced to 2 tablets (800 mg). The tablets should not be crushed, chewed or swallowed with hot liquids. When changing from other lithium preparations, serum lithium levels should be first checked, then PRIADEL therapy commenced at a daily dosage as close as possible to the dosage of the other form of lithium.

2. Four to five days after starting treatment (and never longer than one week), a blood sample should be taken before the daily dose of tablets for the estimation of serum lithium levels.

3. If necessary, the dose of PRIADEL is adjusted by half to 1 tablet to maintain serum lithium levels between 0.6–1.5 m.mol/L (=mEq/L). Serum lithium levels should be monitored on a weekly basis until stabilisation is achieved.

4. Following stabilisation of serum lithium levels, the time interval between subsequent estimations can be gradually increased, but should not normally exceed three months.

5. Careful clinical appraisal of the patients should be exercised throughout medication.

6. Priadel should be continued through any recurrence of the affective disturbance. This is important as the full prophylactic effect may not occur for 6–12 months after the initiation of therapy.

7. Thyroid function tests should be performed approximately once yearly. A small number of patients may show drug induced hypothyroidism which may be treated successfully with concurrent thyroxine.

Treatment of acute mania and hypomania: It is likely that a higher than normal PRIADEL intake may be necessary in the acute phase. Therefore, as soon as control of the mania is achieved, the serum lithium level should be determined and it may be necessary dependent on the results, to lower the dosage of PRIADEL and re-stabilise serum lithium levels. In all other details, the described treatment schedule is recommended.

Prophylaxis against recurrent mania and hypomania, manic depressive illness, recurrent depression and treatment of depression: It is recommended that the described treatment schedule is followed.

Contra-indications, warnings, etc When contemplating Priadel therapy ascertain whether patients are receiving lithium in any other form; if so check serum levels before proceeding. It is important to ensure that renal function is normal; if necessary a creatinine clearance test or other renal function tests should be performed. Renal insufficiency, cardiac insufficiency, Addison's disease and frank hypothyroidism are all contra-indications to lithium therapy. Treatment should be discontinued during any intercurrent renal infection and should only be reinstituted when kidney function has returned to normal.

Caution should be exercised to ensure that diet and fluid intake are normal, thus maintaining a normal electrolyte balance. This may be of special importance in very hot weather. Infectious diseases including colds, influenza, gastro-enteritis and urinary infections may alter fluid balance and thus affect serum lithium levels.

Although there are reports of the safe use of PRIADEL during pregnancy it is recommended as a general rule that PRIADEL be discontinued during a planned or confirmed pregnancy. If it is considered essential to maintain Priadel treatment during pregnancy serum lithium levels should be closely monitored since renal function alters gradually during pregnancy but suddenly at parturition, thus requiring dosage adjustments. Babies may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Lithium is secreted in breast milk and bottle feeding is recommended.

Side-effects: Transient side-effects may occur during during the stabilisation but are unlikely to do so at serum lithium levels below 2.0 m.mol/L. They are most commonly a fine tremor of the hands, mild polydipsia, mild polyuria, initial anorexia, some loosening of the stools and, more rarely, nausea or diarrhoea. In these cases it is advisable to check serum lithium levels. Weight gain or oedema may present in some patients.

Toxic effects: Such effects are indicative of impending lithium intoxication and they fall into two groups:

a) Gastro-intestinal: increasing anorexia, diarrhoea and vomiting.

b) Central nervous system: mild drowsiness and sluggishness increasing to giddiness with ataxia, coarse tremor of the extremities and lower jaw, tinnitus, blurred vision, muscular twitching, dysarthria progressing (above 2–3 m.mol/L) to seizures, coma and death.

If any of the above symptoms appear, the patients should be instructed to stop taking their tablets and report for an immediate serum lithium estimation.

Lithium intoxication: There is no specific antidote to lithium poisoning. In the event of accumulation lithium should be stopped and serum estimations should be performed every six hours to ensure that the lithium level is falling at a rate corresponding to a half life of under 30 hours.

Under no circumstances should a diuretic be used. Promote osmotic diuresis (Mannitol or urea infusion) or alkalinisation of the urine (sodium lactate or sodium bicarbonate infusion). If there is a deterioration in the patient's condition or if the serum level is over 4.0 m.mol/L, peritoneal or haemodialysis should be promptly instituted. This should be continued until the level of lithium in the serum or dialysis fluid. Serum lithium levels must be monitored for at least a further week to take account of any possible rebound in serum lithium levels as a result of diffusion from body tissues.

Drug interactions: Any drugs affecting electrolyte balance (e.g. diuretics, appetite suppressants, steroids) may alter lithium excretion and should be avoided in patients on lithium. If other psychotropic drugs are used they should be initiated at a lower dosage than usual as their side-effects may be potentiated by the use of lithium. This has been shown to be of particular importance for the concurrent use of lithium and haloperidol.

Pharmaceutical precautions Cool conditions of storage required. Tablets should not be crushed nor any attempt made to dissolve them before administration.

Legal category POM.

Package quantities Tubes of 100 and 1,000 tablets. Fibre drums of 10,000 tablets.

Further information Nil.

Product licence number 0357/5000.

CAMCOLIT*

Presentation *Camcolit 250:* White uncoated tablets, engraved on one side 'Camcolit' each containing 250 mg Lithium Carbonate BP (equivalent to 6.8 millimoles).

Camcolit 400: White uncoated tablets, engraved one side 'Camcolit S' with break line on reverse side, each containing 400 mg Lithium Carbonate BP (equivalent to 10.8 millimoles).

Uses Treatment and prophylaxis of mania, manic-depressive illness and recurrent depression.

Dosage and administration Tablets for oral administration.

Treatment of mania and hypomania: The requisite daily dosage may be administered at the discretion of the clinician, either in divided doses or as a single daily dose. Some clinicians prefer to prescribe Camcolit 250 for divided doses and Camcolit 400 for a single daily dose regime.

Treament of mania should be initiated in hospital where regular monitoring of plasma lithium levels can be conducted.

The dosage of Camcolit should be adjusted to produce a plasma lithium level between 0.6 and 1.2 mmol/l. The required plasma lithium level may be achieved in one of two ways, but whichever is adopted regular estimations must be carried out to ensure maintenance of levels within the therapeutic range. For consistent results it is essential that the blood samples for plasma lithium estimations are taken 12 hours after the last dose of lithium.

1. 1,500–2,000 mg of lithium carbonate are administered daily for the first five or seven days. A blood sample for plasma lithium estimation is taken 12 hours after the last dose on the fifth or seventh day, and the dosage of Camcolit is adjusted to keep the plasma lithium level within the therapeutic range.

Subsequently, regular plasma lithium estimations must be carried out and, where necessary, the dosage of Camcolit adjusted accordingly.

The precise initial dose of lithium should be decided in the light of the age and weight of the patient; young patients often require a dose higher than average and older patient a lower dose.

2. A lithium clearance test is carried out and the initial dosage calculated from the results. Even when the initial dosage is calculated in this way, it is still desirable that plasma lithium levels should be determined at weekly intervals during the first three weeks of treatment, and any necessary adjustments to dosage made as a result of the levels actually obtained.

Most of the above applies in the treatment of hypomania as well as mania, but the patient if not too ill can be started on treatment as an outpatient provided that facilities for periodic plasma lithium monitoring are available.

Prophylaxis of recurrent affective disorders (including unipolar mania, unipolar depressions and bipolar manic-depressive illness): Treatment of inpatients can be initiated as described above under 'Treatment of Mania'. If treatment is initiated in outpatients 1,000–1,200 mg of lithium carbonate can be administered daily for the first seven days. A blood sample for plasma lithium estimation is then taken 12 hours after the last dose, and the dosage of Camcolit is adjusted to keep the plasma lithium level within the effective range.

Since lithium can impair thyroid function, it is desirable in patients being treated prophylactically that some screening test of thyroid function, such as the protein-bound iodine test, be carried out at about three-monthly intervals. Many of the initial symptoms of hypothyroidism are similar to symptoms seen in depression, and hence it is difficult to differentiate except by some such screening of thyroid function.

In all cases, plasma lithium levels should be determined frequently and, even when consistent levels have been achieved in prophylaxis, should be monitored at least every 10 weeks.

Contra-indications, warnings, etc The first consideration in lithium therapy is the selection of proper candidates. The second is the physical state of the patient, which must be adequate to handle the lithium ion when it is introduced into the body.

Before administering lithium the clinician must make certain that both the cardiovascular and renal systems are functioning adequately by a careful physical examination, including an ECG if necessary. Lithium is contra-indicated in severe renal disease.

Because lithium can impair thyroid function, it is desirable that some screening test, such as protein-bound iodine, be carried out.

Diuretics reduce lithium clearance, consequently lower doses of lithium may be needed in patients receiving diuretics. Frequent monitoring of the plasma lithium level is essential in these patients. Dosage may need adjustment when there is sodium loss or impaired renal function as in exposure to extreme heat, vomiting, intercurrent infection, or urinary tract infection or disease.

Lithium crosses the placental barrier in animals and has been reported to interfere with fertility, gestation and foetal development in several non-human species.

In 1976, a register of babies born to women receiving lithium for varying times during their pregnancies, revealed that of 160 babies, 18 had malformations, of whom 13 had malformations of the cardiovascular system.

Consequently lithium is contra-indicated in the first trimester.

Should the clinician accept the risk of administering lithium during pregnancy he should note that there have been cases of women who were previously completely stabilised on lithium, developing lithium intoxication at the time of delivery.

It would seem wise to consider a diagnosis of lithium toxicity in all hypotonic infants born to mothers receiving lithium and it is important to ensure adequate fluid and mineral intake during the first few days of life.

Bottle-feeding should be considered for children of women on lithium treatment.

Side effects: Three kinds of side-effects can occur.

1. Transient and harmless symptoms, which usually pass after two or three months of treatment. They include nausea, loose stools, fine tremor of the hands, polyuria and polydipsia.

2. The second type of side-effect is also harmless but inconvenient in that it tends to persist. It also includes fine tremor of the hands, polyuria and polydipsia, but weight gain and oedema may also occur.

Some studies suggest that the tremor can be controlled by relatively small doses of propranolol.

3. The third type comprises a group of severe reactions which indicate impending intoxication. It includes vomiting, diarrhoea, coarse tremor of the hands (which can be easily distinguished from the fine tremor seen as a harmless side-effect), sluggishness and sleepiness, vertigo and dysarthria.

Development of goitre and sometimes hypothyroidism are infrequent complications of lithium therapy and it has been suggested that lithium acts only as a triggering agent for latent hypothyroidism in predisposed patients. These are easily controlled by administration of small doses of thyroxine (0.05–0.2 mg daily) concomitantly with lithium.

Pharmaceutical precautions Store in a cool dry place.

Legal category POM.

Package quantities *Camcolit 250:* 100 and 1,000 tablets.
Camcolit 400: 100 and 500 tablets.

Further information The Authors of a recent comparison between Camcolit and two types of 'slow-release' or 'controlled-release' lithium concluded that there was no significant difference in humans in the rate of absorption or excretion of the different products.

A second study demonstrated that patients who had been receiving their daily dose of lithium carbonate in the form of a 'controlled release' preparation could be changed to the same daily dose of lithium carbonate in the form of Camcolit 400 without significant change in plasma lithium levels or clinical condition.

Product licence numbers
Camcolit 250 0322/5000
Camcolit 400 0322/5015

from our files

RECENT DEVELOPMENTS WITH LITHIUM

Clinical studies update

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From our files

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SIDE-EFFECTS OF LITHIUM

☐ Update on Kidney Damage

At a recent meeting of the Scandinavian Society for Psychopharmacology, 3 more reports were made on impaired kidney function and biopsy-confirmed renal pathology in patients on lithium. The data were preliminary but they indicate a 15-20% incidence of renal pathology in patients treated with lithium. As the kidney lesions progress slowly there is little risk that terminal azotaemia would develop. Because of decreased urine concentrating ability, however, there is an increased risk of dehydration and lithium intoxication. Patients who become polyuric must therefore be advised to drink plenty of fluids. Periodic renal function tests are recommended for all lithium-treated patients. All valuable drugs may do harm as well as good. Although physicians must protect patients from the adverse effects of medicines, they must also protect them against the ravages of untreated or inappropriately treated illness. This entails weighing the risks of treatment against the harm of no treatment.

'Lithium is too valuable a drug to be abandoned at this stage of our knowledge of its potential adverse effects . . . The best service we can provide patients is to master the art of lithium therapy; not to succumb to the expediency of rejecting a therapy that has and still can benefit untold victims of affective disorders, their families and society,' advises the editor of the International Drug Therapy Newsletter.

International Drug Therapy Newsletter 13: 17 (May 1978) (Inpharma 13 May 1978 p.5)

☐ And Long-Term Treatment May Impair Renal Concentrating Capacity

Long-term (2 months to 11 years) treatment of 60 patients with lithium resulted in impaired renal concentrating capacity compared with 30 healthy subjects. Nineteen of the 60 had been treated with lithium alone and 41 in combination with neuroleptic drugs. Renal concentrating capacity was impaired in 25 subjects who had received neuroleptic drugs alone. Two months after lithium was withdrawn renal concentrating capacity improved more in patients who had received lithium alone than in those who had lithium combined with neuroleptic drugs. As total lithium dose increased, osmolality decreased, and was impaired in all 13 patients who had received more than 600g of lithium.

Simmons, C.A. et al.: Lancet 1: 778 (8 Apr 1978)

LONG TERM LITHIUM — SHOULD CRITERIA FOR ITS USE BE STRICTER?

A study of kidney structure and function in patients on lithium for affective illness has shown reduced concentrating capacity and a unique tubular lesion in biopsy specimens from 5 patients who had been on the drug for 4 and 5 months and 6, 7 and 9 years. The lesion was mainly in distal convoluted tubules and collecting ducts, with proximal tubules showing only minor changes. The most obvious feature was ballooning of cells and vacuolation of cytoplasm, but the additional changes were different from any previously described tubular changes. Three patients who had taken lithium for 6, 7 and 9 years had more advanced changes of the type previously described, including sclerosis of 10-20% of glomeruli, tubular atrophy and interstitial fibrosis. The finding of only tubular changes in early biopsy specimens and of focal nephron atrophy in later ones suggests that the tubular lesion may lead to the focal nephron atrophy seen after prolonged lithium treatment. Serum creatinine and urea were normal in all 5 patients and there were no excess red blood cells or protein in urine so the usual indications for biopsy were absent.

This and other reports 'suggest that criteria for using lithium for long term treatment must become stricter'. If long-term prevention of unipolar depressive episodes with continuous tricyclic drugs does not cause kidney lesions, then if there are no cardiac problems, **'tricyclics may be the treatment of choice for recurring depression while lithium is reserved for bipolar patients'.**

Barrows, G.D. et al.: Lancet 1: 1310 (17 Jun 1978) (Inpharma 1st July 1978, p.4.

LITHIUM INTOXICATION IS A SERIOUS CONDITION

. . . Control of Serum Levels and Regular Renal Assessment Are Recommended to Prevent It

Lithium intoxication was studied in 23 patients, 21 of whom developed intoxication while on a maintenance dosage that had been unchanged for 2 months-12 years. One developed intoxication after only 6 days' treatment and 1 had taken an overdose. Lithium intoxication developed gradually in most patients and was characterised by mental and neurological symptoms. Only 2 patients had gastrointestinal symptoms. There were toxic effects on brain, heart and kidneys. The severity of intoxication seemed to depend on at least 3 factors: serum lithium concentration, length of intoxication and individual tolerance. Intoxication was preceded by disorders of water and electrolyte metabolism in most cases, and water loss due to impaired renal concentrating ability seemed to be a major predisposing factor. 17 patients had renal insufficiency on admission and normal renal function did not return in 5. Renal biopsy in 7 patients showed abnormalities suggesting that a chronic nephropathy, possibly caused by lithium, might also be a predisposing factor.

Sodium chloride infusion did not specifically affect lithium excretion. As some patients developed hypernatraemia, it is not recommended. Haemodialysis is at present the most effective method for removing lithium from intoxicated patients. It should be continued for long enough to attain a lithium concentration below 1 mmol/L after redistribution of lithium in the body. Peritoneal dialysis should be used only when haemodialysis is not possible. Of the 23 patients, 2 died and 2 developed persisting neurological sequelae. Lithium intoxication can best be prevented by control of serum levels and regular assessment of renal function and renal concentrating ability during treatment.

Hansen, H.E. and Amdisen, A.: Quarterly Journal of Medicine 47: 123 (Apr 1978)

after administration of yambolap but uptake increased significantly during exercise, in accord with the animal experiments. At rest the V_E fell but the oxygen percentage of the expired gas was not much altered.

Oxygen uptake increased as exercise performance increased. However, comparison of the Vo_2 values at the same load before and after yambolap administration, revealed a relative decrease. The drug seemed to produce, in every patient, striking changes in exercise tolerance when compared with the placebo response. The time to total recovery became shorter, and the ratio of exercise-time and recovery-time rose significantly, pointing to a better ability of regeneration. The duration of anginal pain was also shorter. The oxygen debt formed after the exercise, was also decreased significantly. Yambolap produced a remarkable reduction in the S-T segment depression compared with the placebo response.

We think that this drug might be effective in angina pectoris. It probably acts by influencing energy utilisation at a subcellular level, and in this respect would not be comparable to beta-blockers or nitrates.

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LIMITATIONS OF COMMERCIAL TEST FOR ANTIBODY TO HEPATITIS A VIRUS

SIR,—During a prospective study on consecutive cases of acute viral hepatitis a commercial test ("HAVAB", Abbott) for antibody to hepatitis A virus (HAAb) was evaluated.

Specimens with high IgM but low IgG titre[1] gave low titres which were not reduced after cleavage of IgM antibodies with 2-mercaptoethanol[2] (see table). High titres were obtained with specimens with high IgG titres, which, however, demonstrated lower sensitivity of the Abbott test. Thus the test measures IgG, not IgM, and the manufacturers have confirmed this.

HAAb TITRES BY FLEHMIG AND ABBOTT RADIOIMMUNOASSAYS IN ACUTE AND CONVALESCENT SERA FROM TWO PATIENTS (A AND B) WITH HEPATITIS A

Serum	HAAb titre		
	Flehmig[1]		Abbott (before/after 2-M.E.)†
	IgM	IgG	
A: acute (day 15)	319 000	2600	40/20
A: convalescent (day 96)	100 000	32 000	80/160
B: acute (day 7)	600 000	7500	20/10
B: convalescent (day 107)	80 000	67 000	640/640
Control*	53 000	150	1/<1

*IgM positive; IgG almost negative.
†2-mercaptoethanol treatment.

(The HAVAB test does demonstrate fractionated HAAb IgM, but fractionation is not included in our routine diagnostic work.) It might be possible to demonstrate a significant increase in IgG titre between acute and convalescent serum. Abbott recommends titration in duplicate. However, titration in two-fold dilutions from 1:50 to 1:3200 would need twenty-eight beads; at 12·75 crowns per bead the cost per patient in Sweden would be 357 crowns (about £40) merely for beads.

Abbott states that inverse proportionality is achieved between amount of HAAb and counts/min within an appropriate range of concentration. However, we found this range to be too narrow to allow for determination of the titre by interpolation of a single c.p.m., particularly if obtained on an undiluted specimen, within a standard curve. Thus most undiluted serum specimens, positive in the test, reduced the c.p.m. of the standard ^{125}I-HAAb to the same extent as did the positive control HAAb.

The Abbott HAVAB test can be used for studies of immunity but needs modification for diagnostic use.

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1. Flehmig, B. *Bundesgesundheitsblatt.* 1978, 17, 277.
2. Kunz, C., Hofman, H. *Zbl. Bakt. Hyg. I Abt. Orig. A.* 1971, 218, 273.

LITHIUM-INDUCED URÆMIA

SIR,—The nephrotoxic effects of lithium have been known for many years, but the finding that regular treatment may cause renal damage is alarming. In an earlier series[1] we found only moderately reduced renal function in 7 out of 14 patients. In a screening investigation (unpublished) 8 out of 110 patients treated with lithium for more than 6 months had signs of reduced renal function with a highest serum-creatinine of 2·2 mg/dl. We report here a case of probable lithium-induced uræmia in a patient on regular lithium treatment for only 3 years.

The patient is a 54-year-old man. In 1960 he had an isolated incident of nephrolithiasis. From 1964 he had several depressive episodes and treated with antidepressive drugs for the next 10 years. He was put on lithium in 1974, and from 1974 to 1977 lithium sulphate was his only drug. Renal function and blood-pressure had been normal and there had been no proteinuria in 1972, 1974, or 1976. During lithium treatment he had daily urine volumes of 3–4 litres, but in the summer of 1977 urine volumes up to 8–10 litres were recorded. The serum lithium was measured every 1–2 months. Once, in December, 1975, it was 1·4 mmol/l, but every other routine measurement was below 1·1 mmol/l. When serum-lithium was measured in September, 1977, because of symptoms of tiredness and increasing urine volumes, the value was 2·1 mmol/l, although the same lithium dose had been administered all the time (lithium sulphate 3·3 g/day [60 mmol/day]). Lithium was stopped for a few days and the lithium concentration rapidly fell. Treatment was then continued at a lower dose (1·7 g/day). In all measurements thereafter serum-lithium was below 1·0 mmol/l. Lithium treatment was stopped in December, 1977, when signs of renal damage were observed. In November, 1977, serum-creatinine was 152 μmol/l, and increased rapidly up to 500 μmol/l late in February, 1978. The glomerular filtration-rate decreased between January and March from 38 to 13 ml/min. Thereafter, the renal function, last measured in November, 1978, has been stable. The blood-pressure was slightly raised in September, 1977, and from November, 1977 he was put on antihypertensive treatment. When admitted in February, 1978, for kidney biopsy he had a slight anæmia, E.S.R. 46 mm/h, and proteinuria of 1 g/day, but no hæmaturia. On X-ray the kidneys appeared to be of normal size; there were no calcifications, no urinary-tract obstructions, but the charging was reported to be decreased.

Renal biopsy revealed severe focal interstitial cortical fibrosis and nephronic atrophy. With our "point count" technique[1] we found 38·4% interstitial fibrous cortical tissue. 4 out

1. Hestbech, J., Hansen, H. E., Amdisen, A., Olsen, S. *Kidney Int.* 1977, 12, 205.

of 18 glomerular sections were totally sclerotic. In the rest of the glomeruli there were no specific changes such as hypercellularity, adherences, crescents, or any other evidence of glomerulonephritis. In the fibrous scars there were atrophic tubular profiles and a focal moderate mononuclear cell inflammation. There was a moderate arteriolosclerosis. The medulla was not represented. immunofluorescence investigation of IgG, IgA, IgM, complement C_3, C_4, properdin, fibrinogen, and properdin A were negative in the glomeruli, but there was an increased amount of C_3 in the interstitium and in the tubular basement membranes.

The clinical picture, with alarming signs of rapidly developing renal insufficiency, and the biopsy findings clearly point to a nephrotoxic disease. The histological picture is very similar to our previously published[1] and unpublished findings from two groups each of 14 patients on long-term lithium. This chronic interstitial nephropathy is unspecific, but there were no symptoms or signs of other causes of nephropathy. The patient's first symptoms of a renal disease were increasing polyuria, a well-known side-effect of lithium. We also consider it significant that the rapid progression of renal insufficiency stopped when lithium treatment was withdrawn. There have been no signs of activity of the disease during the past 8 months. The similarity of the histological picture to our published description of renal lesions in patients on long-term lithium treatment clearly points to lithium as the causative agent. Lithium treatment, even when well controlled, may cause severe renal damage; our patient was on the brink of dialysis treatment before the diagnosis was made.

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LOCAL SNARES IN CORONARY SURGERY

SIR,—The use of the encircling tapes or snares to control blood-flow from the opened right coronary artery during aortocoronary bypass surgery remains quite common, despite the introduction of cardioplegic arrest[1] which should obviate the need for such local control. A local snare has the potential for promoting obstruction and occlusion from plaque fracture or subintimal hæmorrhage and this danger should be worst with the distal right coronary artery, which is usually heavily and diffusely arteriosclerotic and often calcified. Figs. 1 and 2 illustrate just such a case of iatrogenic occlusion so that an otherwise excellent operation technically (the graft being patent at both ends) is rendered useless.

This case is not unique, as I have learned from other surgeons, and I believe it is time to condemn the use of local snares in coronary surgery. For those who remain uncomfortable with the use of anoxic arrest, a better technique to control local bleeding is to insert a small balloon-tipped embolectomy catheter attached to a three-way stopcock. The balloon is then inflated to precisely the point at which bleeding stops, and a turn of the stopcock maintains this position. Intraluminal control such as this is far less likely to damage the arterial wall than external crushing with a snare.

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1. Miller, D. W., Hessel, E. A., Winterschied, L. C., Merendino, K. A., Dillard, D. H. *J. thorac. cardiovasc. Surg.* 1977, 73, 75.

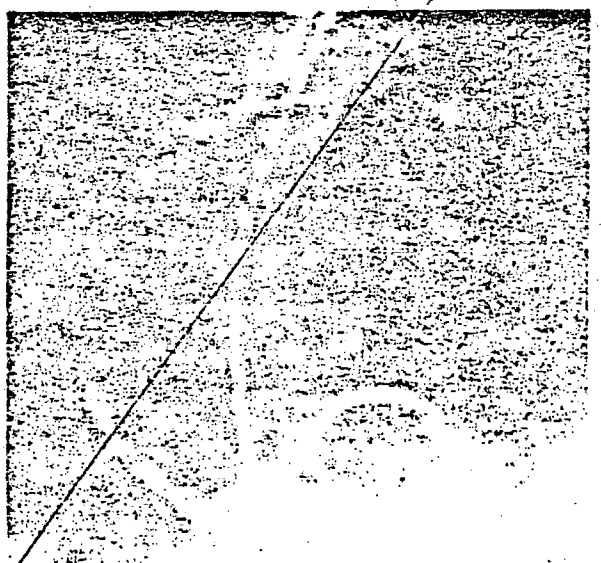

Fig. 1—Preoperative angiogram shows tight proximal occlusion of right coronary artery with no significant distal narrowing.

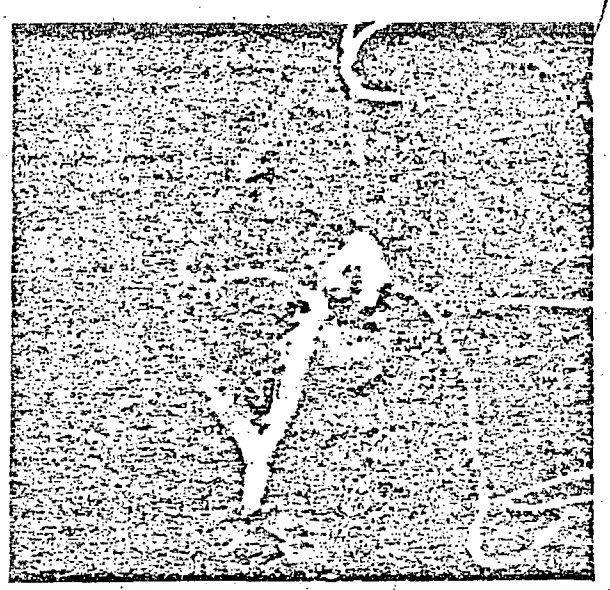

Fig. 2—One month postoperatively distal artery is totally occluded (large arrow) just beyond distal anastomosis.
Graft perfectly patent at both ends. Dye injected into native right coronary flows back up graft into aorta (small arrows indicate direction of flow).

FALSE-POSITIVE PARACETAMOL ASSAY

SIR,—A potential source for false-positive results in the colorimetric plasma-paracetamol method of Glynn and Kendall[1] was uncovered when the remaining contents of a syringe of arterial blood on which a blood-gas assay had just been done were centrifuged to provide plasma for a paracetamol assay. The plasma gave an apparent positive result. Venous blood from the same patient was negative. These findings were confirmed by repeating the tests on the same samples. The arterial sample had been taken into a syringe previously heparinised with a small volume of 25 000 I.U./ml heparin injection (mucous) *B.P.* containing 0·3% v/v cresol (Paines and Byrne) while the venous sample had been put into a lithium heparin tube (Searle).

2. Braimbridge, M. V., Chayen, J., Bitensky, L., Hearse, D. J., Jynge, P., Cankovic-Darracott, S. *ibid.* 1977, 74, 900.

1. Glynn, J. P., Kendall, S. E. *Lancet*, 1975, i, 1147.

Renal function after long-term treatment with lithium

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British Medical Journal, 1979, **1**, 1457-1459

Summary and conclusions

Daily urine volumes, plasma creatinine concentrations, and creatinine clearance were measured in 106 patients with unipolar and bipolar affective disorders attending a "lithium" clinic. Urine volumes exceeded 3·5 l in only six patients, plasma creatinine concentrations exceeded 150 μmol l (1·7 mg/100 ml) in only five, and creatinine clearance was below 50 ml/min in 16. Renal function was assessed by measuring creatinine clearance and renal tubular function, including response to 20 hours of water deprivation, in a representative sample of 30 patients from the lithium clinic and 30 psychiatric patients matched for age and sex who were taking other psychotropic drugs. Creatinine clearance and tubular function, including urine osmolality after water deprivation, were not significantly different between the two groups. Urinary excretion of arginine vasopressin (AVP), however, was much greater in the lithium-treated patients, who therefore had a diminished tubular responsiveness to AVP.

The findings do not support suggestions that long-term lithium treatment results in seriously impaired renal function, renal damage, and polyuria. Compared with other series, however, the patients were being maintained with low serum lithium concentrations, which apparently are as effective prophylactically as higher concentrations.

Introduction

Long-term treatment with lithium may cause polyuria[1] associated with an increase in plasma antidiuretic hormone (ADH),[2] and it is therefore due wholly or largely to diminished renal responsiveness to ADH. The polyuria is troublesome but not serious. Recent reports,[3] however, suggest that lithium reduces the glomerular filtration rate and causes a focal interstitial nephropathy.[4] Such reports cast doubt on the future use of lithium in the long-term treatment of recurrent affective disorders.

We have measured the daily urine volumes and creatinine clearance in 106 patients attending our "lithium" clinic. Thirty of these patients and 30 patients matched for age and sex who were taking other psychotropic drugs were admitted overnight and investigated for creatinine clearance and several renal tubular functions, including urine osmolality after water deprivation.

Patients and methods

Table I gives the details of 123 patients attending the clinic. All were asked to collect urine for 24 hours, ending at 0800 on the day of their next routine visit. Verbal and written instructions on how to collect the urine had been given to each patient at the previous visit. Only 24-hour collections containing over 80% of the daily lithium dose were accepted as complete. If the collection contained less than this it was repeated once after further instructions and explanations. A total of 106 patients produced a satisfactory collection.

TABLE I—*Details of 123 patients attending lithium clinic*

	Age (years)		Duration of lithium treatment (months)	Serum lithium concentration 12 hours after last dose (mmol l)	Dosage of lithium carbonate (mg)
	Men (n = 49)	Women (n = 84)			
Mean ± SD	55·6 ± 13·7	54·2 ± 12·9	74·1 ± 38·8	0·59 ± 0·17	802·5 ± 290·0
Range	21-81	19-77	6-180	0·31-1·07	250-2000

Conversion: SI to traditional units—Serum lithium: 1 mmol l = 0·7 mg/100 ml.

We selected as a representative sample 30 patients who had been taking lithium for a mean of 8·3 ± SD 2·8 years (range 3·0-12·4 years) and 30 psychiatric patients matched for age and sex with the lithium group who were taking psychotropic drugs other than lithium. Patients and controls were admitted in random order to the research unit and stayed from 1800 till 1500 the next day. Subjects took no medication from 18 hours before admission until the end of the test except for 5 mg nitrazepam on retiring to bed. Throughout their stay patients were supervised by the nursing staff of the unit, who ensured that they took no food or drink and that all urine was collected. The patients were accurately weighed at 1900, 0700, and 1500. Blood samples were taken, without stasis, at 0900 and 1400 into strontium-heparin tubes, which were stoppered so that no air was trapped above the blood. Urine was collected over 18 hours from 1900 to 1300 and used to measure creatinine clearance. A further, two-hour urine sample, collected between 1300 and 1500, was used to assess tubular function.

Plasma sodium, potassium, calcium, and bicarbonate concentrations and plasma and urine creatinine and phosphate concentrations were measured on a Vickers M300 multichannel analyser. Urine osmolality was measured on an advanced osmometer; urine β_2-microglobulin was measured by radioimmunoassay (Phadebas), and arginine vasopressin (AVP) was measured by a specific and sensitive radioimmunoassay.[5] Urine AVP was expressed as osmolar clearance (pg/ml), which is closely related to plasma AVP.

Glomerular function—Creatinine clearance was calculated from creatinine excretion in the 18-hour urine collection and the creatinine concentration in the 0900 plasma sample.

Tubular function—Tubular reabsorption of small-molecular-weight proteins was assessed from the excretion of β_2-microglobulin in urine. The maximum tubular reabsorption capacity for phosphate per unit of glomerular filtration rate (GFR) was calculated from the phosphate and creatinine concentrations in plasma and urine.[6] Tubular reabsorption of water was assessed from the 24-hour urine volume in the large group and from the urine osmolality and weight loss after water deprivation for 20 hours in the smaller groups. In the smaller sample the relation between urine AVP and urine osmolality was used to assess tubular responsiveness to AVP.

Results

Only six of the 106 lithium-treated patients had a 24-hour urine volume exceeding 3·5 l, and six (five had a plasma creatinine concentration above 150 μmol l (1·7 mg/100 ml); two of these patients had both an increased urine volume and a raised plasma creatinine concentration. The 24-hour creatinine clearances were very variable (30 to 165 ml/min; mean 75·7 ± SD 30·2 ml/min). Thirty-eight patients had a creatinine clearance below 70 ml/min, and in 16 it was below 50 ml/min.

Table II shows the various assessments of renal function in the

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smaller, selected lithium group and controls. The two groups had similar mean plasma creatinine and creatinine clearance values. Many patients in each group had low creatinine clearance values: to controls and 16 lithium-treated patients had values below 70 ml/min, and 6·0 of the controls and 13 patients in the lithium group had clearance values below 50 ml/min. Except for two patients in the lithium group, however, the plasma creatinine concentration was normal in all patients.

TABLE II—*Renal function in lithium-treated and control patients. Values are means ± SD*

	Lithium group (n = 30)	Control group (n = 30)
Urine volume over 18 hours (ml)	1573 ± 169	1209 ± 62
Creatinine clearance (ml/min)	61·1 ± 30·2	81·3 ± 52·0
Plasma creatinine (μmol/l)	93 ± 29	84 ± 15
Phosphate clearance (ml/min)	15·6 ± 8·4	17·0 ± 7·9
Phosphate: creatinine clearance ratio	0·29 ± 0·13	0·25 ± 0·15
β_2-microglobulin (ng/l)	213 ± 206	220 ± 200
β_2-microglobulin (μg/h)	11·8 ± 11·4	13·0 ± 14·6
Values after 20 hours of water deprivation:		
Osmolality (mmol/kg)	509 ± 193	579 ± 207
Weight loss over 12 hours (kg)	1·19 ± 0·50	1·27 ± 0·92
Log urine AVP	1·693 ± 0·34	1·098 ± 0·47
Urine AVP (pg/min)	77·7 ± 72·5	21·2 ± 21·5
Urine AVP (pg/ml)	49·3 (18-136 (± 1SD); 6·5-374 (± 2SD))	12·5 (4·3-37 (± 1SD); 1·4-109 (± 2SD))

Conversion: SI to traditional units—Plasma creatinine: 1 μmol/l ≈ 0·01 mg/100 ml. Osmolality: 1 mmol/kg = 1 mosmol/kg.

Urinary excretion of β_2-microglobulin and tubular reabsorption of phosphate were similar in the two groups, as was the weight loss during water deprivation and the urine osmolality at the end of water deprivation. Urinary excretion of AVP, however, was much greater in the lithium-treated group.

Table III gives the plasma electrolyte, urea, and creatinine concentrations after water deprivation in the two groups. No significant differences were observed.

TABLE III—*Mean plasma values ± SD after 20 hours of water deprivation in lithium-treated and control patients*

	Lithium group (n = 30)	Control group (n = 30)
Sodium (mmol/l)	141·4 ± 3·6	140·0 ± 3·2
Potassium (mmol/l)	4·19 ± 0·24	4·08 ± 0·37
Calcium (mmol/l)	2·65 ± 0·16	2·61 ± 0·11
Bicarbonate (mmol/l)	23·9 ± 1·9	26·8 ± 3·3
Urea (mmol/l)	4·97 ± 1·17	4·71 ± 1·17
Creatinine (μmol/l)	92·8 ± 28·8	83·8 ± 15·3

Conversions: SI to traditional units—Plasma sodium, potassium, and bicarbonate: 1 mmol/l = 1 mEq/l. Plasma calcium: 1 mmol/l ≈ 4·0 mg/100 ml. Plasma urea: 1 mmol/l ≈ 6·0 mg/100 ml. Plasma creatinine: 1 μmol/l ≈ 0·01 mg/100 ml.

Discussion

Of the 106 patients receiving long-term lithium treatment, only six had polyuria, and detailed study showed that as a group they could increase their urine osmolality as much as the controls during water deprivation. Urinary AVP in the lithium group, however, was higher for any urine osmolality than in the control group, which suggests diminished responsiveness and confirms the findings of Bayliss and Heath.[8]

There was no evidence of any deterioration in GFR due to lithium. Although the GFR as assessed by endogenous creatinine clearance was perhaps low on average compared with generally accepted standards, it was not lower in the lithium group than in a group matched for age and sex taking other psychotropic drugs. Hestbech *et al*[4] reported that patients receiving long-term lithium treatment have a reduced GFR and interstitial nephropathy. Hansen and Amdisen,[5] who investigated 21 patients who had developed intoxication during long-term treatment with lithium at a dosage of 1 mmol/kg/day (0·15 mg/kg/day) reported that water loss due to impaired renal concentrating ability seemed to be a major predisposing factor for intoxication. In seven patients renal biopsy showed abnormalities suggesting a chronic nephropathy, possibly caused by lithium, which might be another predisposing factor. Hestbech and Amdisen[6] reported a case of probable lithium-induced uraemia in a patient given regular lithium treatment for only three years; they also found that eight out of 110 patients treated with lithium for more than six months had signs of reduced renal function. Abnormal histological findings in the kidneys of lithium-treated patients were confirmed by Burrows *et al*,[7] who also reported an additional unique tubular lesion in patients taking lithium. Other[9] workers[10 11] found that long-term lithium treatment damages the kidney, but some of the patients examined had had previous episodes of lithium intoxication and many had severe polyuria.

Our failure to find a reduced GFR in the lithium group could be due to error in measuring GFR from creatinine clearance, use of an inappropriate control group, or a real difference between our lithium-treated patients and those investigated by others. Abnormal glomerular function is difficult to detect with creatinine clearance because of errors in urine collection and the large variability in normal clearances, particularly with age. Nevertheless, whereas the urine collections may have been incomplete in the outpatients despite the precautions taken, this is most unlikely to have been the case in the inpatients because of the personal supervision. In any event none of these problems would explain our failure to find a difference between the lithium and control groups. Our controls were taking psychotropic drugs other than lithium and might themselves have had diminished renal function. The use of such a control group, however, can be justified since the treatment for recurrent affective disorder is not lithium or nothing but antidepressant drugs with or without anti-mantic drugs given symptomatically for each episode of affective illness. It may, indeed, be argued that it was not appropriate to choose donor kidneys not used for transplantation as the control specimens for histological studies.

There was, however, a major difference between our lithium-treated patients and those investigated by others—namely, we used smaller and divided doses of lithium. In a study by Hestbech *et al*[4] five out of 14 patients had had previous episodes of lithium intoxication and the average 12-hour serum lithium concentration for the whole group was 0·94 ± SD 0·09 mmol/l (0·65 ± SD 0·06 mg/100 ml), which was much higher than the average concentration used by us (0·59 ± 0·17 mmol/l; 0·41 ± 0·12 mg/100 ml). Our method of management was also associated with a lower incidence of polyuria and hypothyroidism. Only 6 (5·7%) of our 106 patients had polyuria, whereas this occurs in over 50% of patients in other centres.[3] Only 9 (8·5%) of our patients had hypothyroidism,[12] defined as a definite and persistent rise in thyrotrophic hormone, whereas this occurs in 13-33%[13-15] of patients in other centres. Our doses were adequate for prophylaxis, however, as there was no increase in the frequency of clinical relapse in patients with unipolar or bipolar disorders treated with long-term lithium until the 12-hour plasma lithium concentration fell below 0·4 mmol/l (0·3 mg/100 ml), when the yearly frequency of relapse increased from 10-15% of patients to over 50%.[16]

These findings support the suggestion that the lack of significant effects of lithium on renal function in our patients was due to our use of smaller but equally effective doses of lithium. Nevertheless, since it is common to continue lithium treatment for many years, if not indefinitely, and because of nephrotoxic effects of other drugs such as analgesics take a decade or so to develop, longer observations will be necessary even at the smaller doses before lithium can be exonerated of any agent that might produce unwanted effects on the kidney.

We thank the nursing staff of the research unit and the technicians of the pathology department at Hope Hospital for their help in the investigation. Dr. Peter Hestbech, Medical Department M, Aarhus Kommunehospital, Aarhus, Denmark, kindly provided us with information on the Danish experience. This work was supported by a grant from the Medical Research Council.

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SHORT REPORTS

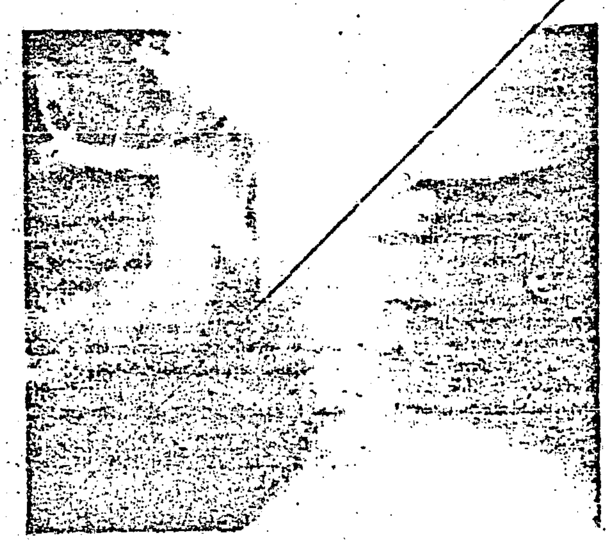
Pyogenic meningitis due to a vertebral abscess

Cervical vertebral abscess is a rare cause of meningitis. Diagnosis may be difficult as its symptoms and signs may be overshadowed by those of meningitis, as shown in the following case.

Case report

A 47-year-old man was admitted in September 1978 with a history of headaches for two weeks, deteriorating vision for five days, and nausea and vomiting for two days. Three months earlier he had fallen in the snow, hurting his left shoulder, and since then he had had constant pain in the left shoulder, radiating to the left side of his neck and to the occipital region. He had suffered from night sweats and had lost 13 kg. His neck had been stiff for about two months. In June 1969 he had been treated for an extensive carcinoma of the pyriform fossa with radical cobalt radiation.

On examination he was obese, fully conscious and orientated, but aggressive and in pain. His temperature was 38·4°C; he had appreciable neck stiffness, a positive Kernig's sign, bilateral papilloedema, and small pupils. There were no focal neurological signs. A computerised axial tomographic scan was normal. Lumbar puncture showed a cloudy cerebrospinal fluid which contained 1·71 × 10⁹ white cells/l (95% polymorphs and 5% lymphocytes); protein 1 g/l and glucose 0·5 mmol/l (9 mg/100 ml). A Gram stain showed no organisms and culture was negative. Radiographs of his cervical spine showed only minor degenerative changes.



Radiograph of cervical spine showing erosion of anterior margins of fourth and fifth cervical vertebrae.

He was treated with analgesics and high doses of penicillin and sulphadiazine and dexamethasone. Although he improved symptomatically with the loss of his headache, he continued to have neck stiffness and he remained feverish after two weeks of chemotherapy. Radiography of his cervical spine with tomography now showed erosion of the anterior margins of the fourth and fifth cervical vertebrae adjacent to the disc, together with narrowing of the disc space and soft tissue swelling at this level (see figure). A technetium scan showed a high diffuse uptake throughout the cervical spine.

He then developed weakness of the right arm and signs of cord compression at C4-5 and his general condition deteriorated. An exploration of the neck was performed through an anterior approach and necrotic material was aspirated from the disc space between C4 and C5. Bilateral ventricular drains were inserted. Bacteriological examination of the aspirate showed numerous neutrophils, Gram-positive cocci, and Gram-negative rods. Culture of both aspirate and ventricular cerebrospinal fluid showed a heavy growth of β-haemolytic streptococci and Bacteroides melaninogenicus; both organisms were sensitive to penicillin. Fifty days after admission he died.

Necropsy showed evidence of a severe meningitis. The bodies of the fourth and fifth cervical vertebrae were collapsed and the centres were necrotic and infected. Pus communicated with the spinal canal through a hole in the posterior longitudinal spinal ligament which had been eroded at this level. Histological examination showed an acute purulent meningitis and the remains of an abscess within the fourth and fifth cervical vertebrae. There was no evidence of carcinoma affecting the cervical vertebrae.

Comment

The history of neck pain, night sweats, and weight loss, together with the presence of severe neck stiffness which was out of proportion to the other signs of meningitis, suggested the possibility of a cervical spine abscess. Normally a bone scan with technetium-99m is useful in diagnosing spinal osteomyelitis: in a series reported by Frederickson et al[1] a scan was positive in 12 out of 12 patients with spinal abscesses. But in our patient the diffuse isotope uptake in the cervical spine and the presence of meningitis obscured the underlying abscess. Changes on radiographs of the spine occur late, and in this patient convincing evidence of an abscess was obtained only after tomography.

The organisms isolated from this patient's abscess and cerebrospinal fluid were unusual and were common throat commensals. [illegible] probably grew in an area of irradiation [illegible] relationship to the previous treatment for carcinoma of the pyriform fossa. It is clearly important to aspirate and culture the pus. Failure of the [illegible] to respond to appropriate antibacterial treatment emphasises the importance of early surgical drainage when a spinal abscess is associated with meningitis.

1 Frederickson, B, Yuan, H, and Olans, R, [illegible] 131, [illegible]

(Accepted [illegible])

Royal Infirmary, Sheffield

CHRISTINE HOYLE, [illegible] physician
W R TIMPERLEY, [illegible] consultant neuropathologist
J F MADDOCKS, [illegible] consultant physician

Annex 4

in digital vessel patency rates between 15°C and 21°C justify using this thermal stress.

In our patients plasma exchange significantly improved digital vessel patency rates at both 15°C and 21°C. Plasma exchange is known to be a potent method of defibrination.[15] Furthermore, plasma fibrinogen is a major determinant of whole blood viscosity at low shear rates. Thus the concept that narrowed digital vessels, initially impassable to viscous blood, are able to transmit blood rendered less viscous by plasma exchange appears attractive. Nevertheless, like Browse[16] we cannot explain why short-term reduction in plasma fibrinogen concentrations results in a long-term symptomatic improvement, and, in our patients, also quantitative evidence of improvement. This long-term improvement may be explained partly by changes which have been observed in the deformability of the red blood cells,[17] but the possible role of circulating immune complexes[7] still needs clarification and is the subject of continuing investigation.

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Indomethacin increases plasma lithium

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Summary and conclusions

The effects of indomethacin on plasma lithium concentrations and renal lithium clearance were investigated in three psychiatric patients and four normal volunteers. After steady-state plasma lithium concentrations had been reached, the subjects received indomethacin placebo for three to seven days, indomethacin (50 mg thrice daily) for seven days, and placebo again for three to seven days. Indomethacin increased plasma lithium concentrations by 59% in the psychiatric patients and 30% in the volunteers. Renal lithium clearance was reduced by indomethacin by 31% in the group as a whole, and prostaglandin synthesis, determined by measuring the major metabolite of PGE_2 with mass spectrometry, was reduced by 55%.

These results show that indomethacin reduces renal lithium clearance to an extent which may be clinically important. They also suggest that the renal clearance may be affected by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

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Introduction

Lithium is being given to increasing numbers of patients for the treatment of manic depressive and other psychiatric illnesses.[1] This treatment is not without hazards, and fatal lithium intoxication has been reported.[2] We describe here a drug interaction between lithium and indomethacin which could make the simultaneous administration of these drugs hazardous. We also provide evidence for a novel prostaglandin-mediated excretory mechanism of lithium.

Patients and methods

The study was carried out in three psychiatric patients in the manic phase of their disease and in four normal volunteers. The study was started when steady-state lithium concentrations had been reached, which usually required over three weeks of constant lithium intake in the patients and 10 to 14 days in the normal volunteers. Steady state was defined as plasma lithium concentrations on three consecutive days within 0·1 mmol/mEq/l of each other. The patients and volunteers were kept on free diet throughout the study and received no other drugs.

The study consisted of three periods in which lithium intake was constant. In the first period an indomethacin placebo was given for three to seven days, in the second indomethacin was given in a dose of 50 mg three times a day for seven days, and in the third placebo was given for three to seven days. Throughout the study we determined plasma lithium concentrations daily 12 hours after the last dose and lithium and creatinine in daily 24-hour urine samples. On the last day of each period 7α-hydroxy-5, 11-diketotetranorprosta-1, 16-dioic acid (PGE-M) was determined by gas chromatography-mass spectrometry[3] to assess the rate of prostaglandin synthesis, and each patient underwent psychiatric evaluation on the brief psychiatric rating scale, side-effect scale, and Minnesota personality inventory.

Results

Indomethacin increased plasma lithium concentrations in all the psychiatric patients and volunteers. The average increase in the plasma lithium concentration (average of the last two days on indomethacin) over values in the first placebo period was 39% in the psychiatric patients and 30% in the normal volunteers (fig 1). In all subjects studied plasma lithium values increased by 42±8% (mean±SE; $P<0.01$) and fell in the second placebo period to 116±5% ($P<0.01$) of control (=100%). A representative study in one of the psychiatric patients is shown in fig 2. Indomethacin increased the plasma lithium concentration from 0·95 to 1·5 mmol/l within five days. The patient was switched back to placebo at that point to avoid toxicity and the plasma concentrations promptly declined. Indomethacin also reduced urinary lithium excretion.

Renal lithium clearance was suppressed by indomethacin in all the subjects by an average of 31±3% (fig 3) and tended to return to pre-indomethacin values in the second placebo period.

The values for PGE-M in the three study periods were 8·1±3, 3·7±0·5 ($P<0.01$), and 10·8±3 µg/g creatinine ($P<0.01$).

None of the psychiatric tests showed that indomethacin had any harmful effect.

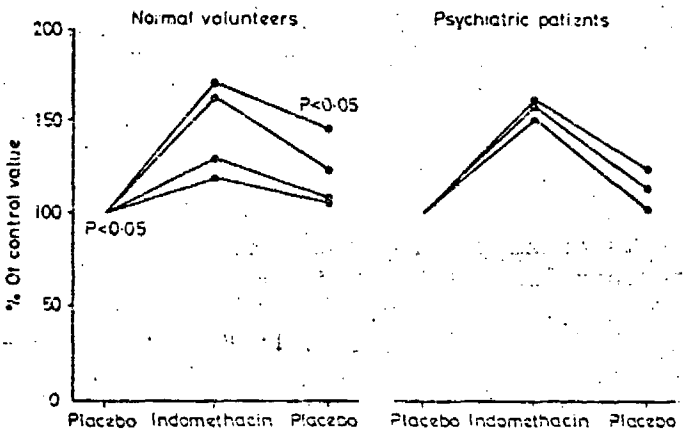

FIG 1—Effect of indomethacin on plasma lithium concentrations in normal volunteers and psychiatric patients.

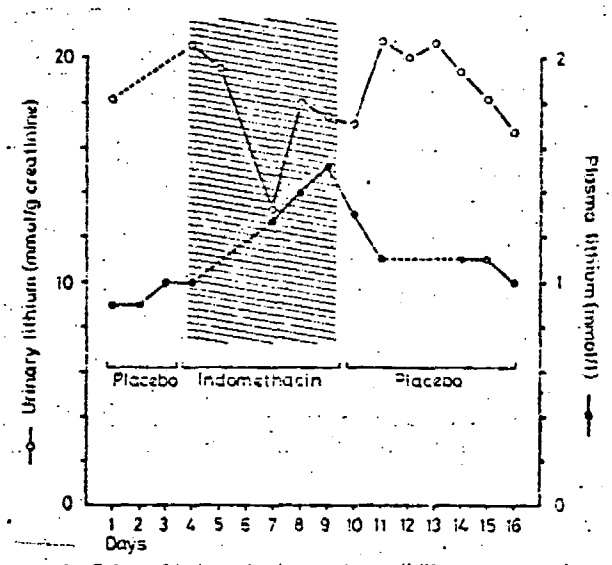

FIG 2—Effect of indomethacin on plasma lithium concentrations and renal lithium excretion in a psychiatric patient.

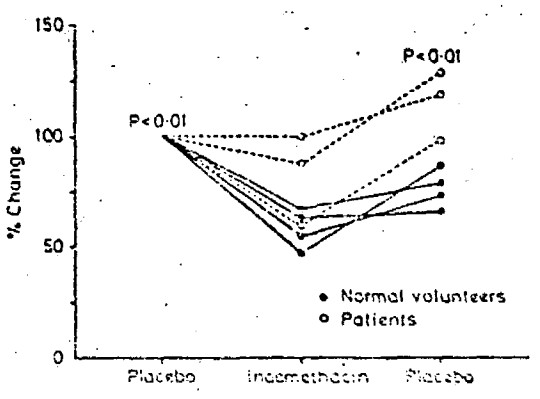

FIG 3—Effect of indomethacin on renal lithium clearance in patients and normal volunteers.

Discussion

Our results show that indomethacin causes a clinically relevant drug interaction with lithium. The increase in plasma lithium concentration was enough to lead to toxicity, and seems to have been caused by a reduction in renal clearance of lithium, since the size of the increase in the plasma concentration corresponded reasonably well to the size of the decrease in renal clearance. The cause of the reduction in renal lithium clearance by indomethacin is obscure. Indomethacin has no effect on glomerular filtration rate in man.[3]

Indomethacin regularly causes sodium retention in man, however,[4] thus suggesting that enhanced sodium and lithium reabsorption might be caused by a similar mechanism. Recent studies on the site of action of prostaglandin synthesis inhibitors such as indomethacin on sodium transport have shown that these inhibitors cause an enhanced medullary sodium concentration.[5] Furthermore, prostaglandin E_2 injected into the distal tubule decreases net distal tubular sodium efflux,[6] and in the isolated cortical collecting tubule peritubular prostaglandin E_2 inhibits sodium transport.[7] All these findings suggest that prostaglandins have an effect on distal tubular transport. Nevertheless, lithium is thought to be reabsorbed only in the proximal tubule[8] because diuretics that decrease distal sodium reabsorption do not enhance lithium excretion.[9]

Our results show that indomethacin reduces renal clearance of lithium to an extent that may be clinically important. They also suggest that the renal clearance of lithium may be influenced substantially by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

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(Accepted 7 March 1979)

Annex 5

ADVERSE INTERACTION BETWEEN LITHIUM AND TETRACYCLINE: Despite its extensive usage, there have been infrequent instances of adverse interactions between lithium and other medicines. To date those that have been reported include interaction with diuretics, antibiotics, and neuroleptics. To this catalogue must be added a potentially serious interaction between lithium and tetracycline. (1). This occurred in a 30-year-old bipolar woman who, for 3 years, had been stabilized by 1600 mg lithium a day producing a serum concentration ranging from 0.5 to 0.84 mEq/l. After developing a vaginal discharge, she was started on tetracycline 250 mg long-acting capsules (Tetrabid - Organon) two as the first dose and one three times a day thereafter. Two days after the start of tetracycline therapy, a routine serum lithium disclosed a dramatic rise to 1.7 mEq/l. Four days after initiation of tetracycline therapy, her speech was slurred, she was slightly drowsy and she had excessive thirst accompanied by a fine tremor of both hands. At that time, her serum lithium was 2.74 mEq/l. Lithium and tetracycline were discontinued. Three and 5 days later her serum lithium concentrations were 1.89 and 0.28/mEq/l respectively. This rapid decline in serum lithium was accompanied by a prompt abatement of all signs of toxicity.

EDITOR'S COMMENT: This is the second published report of an adverse interaction between lithium and an antibiotic; the first was published in the April 1978 issue of this Newsletter. Both of these case reports illustrate the danger of co-prescribing lithium with a drug that may sometimes have a nephrotoxic effect (2). Tetracycline has been known to produce anorexia, nausea, vomiting, sodium diuresis, and polyuria in individuals who already have renal insufficiency. (3). There are two important lessons taught by these cases. These are: (1) a physician should always be on guard when lithium is co-administered with any drug that may affect renal function, even if the drug is an antibiotic; and (2) whenever lithium is co-prescribed with a drug known to affect renal function, serum lithium should be checked within a few days after the combined therapy was started, since the early stages of lithium intoxication are often symptomless.

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In hyperphosphataemic patients aluminium hydroxide therapy must be continued to bind phosphate in the gut and so prevent an increase in plasma phosphorus and consequent soft-tissue calcification.

CONCLUSION - Alfacalcidol and calcitriol have the advantage that the hypercalcaemia they may cause disappears faster when the drug is stopped than with calciferol, cholecalciferol and dihydrotachysterol. This makes alfacalcidol and calcitriol easier to use, particularly in the management of hyperparathyroidism in chronic renal failure. The best choice of drug for any purpose, and the best way of using it, remain unclear.

Basic NHS Costs of 4 weeks' treatment

Alfacalcidol (One-Alpha)	1 mcg daily,	£ 7.00
Strong calciferol tablets BP	2.5 mg daily,	45p
Dihydrotachysterol (AT10)	1 ml daily,	£12.92
(Tachyrol)	0.2 mg daily,	£ 2.58

*Cholecalciferol is not available commercially. Capsules containing 0.25 mg and 1 mg are made by the pharmacy at University College Hospital, Gower Street, London WC1E 6AU. They can be supplied in multiples of 1000, but are not always immediately available.

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RENAL TOXICITY OF LITHIUM

Lithium has been used increasingly for the prevention of episodes of affective disorder, both manic and depressive. It has also been advocated in the management of other psychiatric conditions such as schizophrenia, alcoholism and personality disorder. However, it has a low therapeutic index. In particular, it induces polyuria and polydipsia[1] which may be transient, recurrent or persistent. They are symptoms of nephrogenic diabetes insipidus,[2,3] and are particularly prevalent in patients receiving additional psychotropic drugs.[4] Between 5 and 30% of patients taking lithium suffer from polyuria, depending on dosage, dosage interval and total amount of lithium ingested; it may occur even after short-term treatment. The mechanism is that lithium inhibits the effect of antidiuretic hormone (ADH) on the kidney and so inhibits the ability of the kidney to concentrate urine.

Renal biopsy findings - Lithium toxicity and the nephrogenic diabetes insipidus which it causes are usually regarded as reversible. However, biopsies from patients with these complications show a high incidence of focal glomerular sclerosis, tubular atrophy and/or interstitial fibrosis.[5-8] The impairment of concentrating ability correlates with the histological changes, suggesting that it is a sign of permanent damage. Polyuria increases the risk of dehydration and lithium intoxication, but its relationship to the histological changes is unclear. Also, the changes progress slowly and the risk of death from renal failure is believed to be small.[6,9] In these reports patients had symptoms of toxicity or abnormal renal

function tests before their biopsies. By contrast, biopsies have been carried out on a pair of monozygotic twins maintained on lithium, in one of whom toxic effects had developed. That twin's biopsy showed interstitial fibrosis and his creatinine clearance remained impaired for nine months after lithium was discontinued. The twin who had never shown lithium intoxication had almost normal renal function but his biopsy also showed interstitial fibrosis, suggesting that renal damage can occur without symptoms.[10]

Biopsies have also shown tubular changes, including a unique lesion in the distal tubules and collecting ducts in patients with normal serum creatinine and urea and normal urine.[11] These changes were noted in two patients who had taken lithium for only four and five months, but were more advanced in those who had taken lithium for longer.

Prevention - These findings are worrying. Until more is known about the incidence and long-term effects of these pathological changes lithium should only be used to control recurrent mania, mania alternating with depression and clear-cut recurrent depression; its use in other conditions should be avoided unless undoubted therapeutic benefit can be demonstrated on a trial basis. The choice in patients with recurrent affective disorders is not between lithium and no drug, but between lithium and other psychotropic drugs such as tricyclic antidepressives and antipsychotic agents, all of which have their own problems of long-term toxicity. Nevertheless, a patient should only be maintained on lithium if benefit persists and if attempts to withdraw lithium (at intervals of, say, 3-5 years) are associated with a recrudescence of attacks. The serum lithium concentrations should be kept as low as possible in the therapeutic range.

CONCLUSIONS AND RECOMMENDATIONS - Lithium should not be prescribed unless treatment will be properly monitored. Before starting treatment with lithium, a urine analysis and urine concentration test should be performed and the serum creatinine measured. These should be repeated at intervals of not more than a year. Lithium should be given in twice daily dosage, so that its concentration in the glomerular filtrate will be less than with the same dose given once daily.

Patients should be instructed to report promptly any polyuria or polydipsia, and also attacks of diarrhoea and vomiting (which may predispose to lithium toxicity by depleting body sodium). They should also be advised not to make major changes in their diet without medical advice. Serum lithium concentrations must be measured regularly in all cases. It seems desirable to provide printed information cards for patients on lithium.

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Controlled Studies of the Acute Antidepressant Effects of Lithium

By E. P. WORRALL, J. P. MOODY, M. PEET, P. DICK, A. SMITH, C. CHAMBERS, M. ADAMS and G. J. NAYLOR

SUMMARY **In two randomized double-blind controlled trials on 63 depressed female in-patients subject to recurrent affective disorder (bipolar and unipolar manic-depressive psychosis) lithium was shown to have major acute antidepressant effects. At the end of three weeks lithium produced more uniform improvement than did imipramine; lithium in combination with tryptophan (in the form of Optimax) was superior to tryptophan alone—the latter drug having no discernible antidepressant activity in this group of patients.**

Lithium did not produce an antidepressant effect until the second and third week of both trials.

The most controversial role of lithium in the treatment of manic-depressive illness lies in its use as an acute treatment for depressive episodes. The value of the drug as an acute anti-manic agent and as prophylaxis in the longer term treatment of both unipolar and bipolar illness is now well-accepted.

In some American centres lithium appears to be regularly used as an acute antidepressant in manic-depressive patients. This practice is supported by the results of a number of controlled studies from that country (Mendels *et al*, 1972; Mendels, 1976; Goodwin *et al*, 1972; Noyes *et al*, 1974; Johnson, 1974; and Baron *et al*, 1975) and by one study from Japan (Watanabe *et al*, 1975). By contrast European authorities have considered the drug of little value in the acute treatment of depression (Baastrup, 1969; Schou *et al*, 1971). This view was recently reiterated by Hullin, who stated when referring to the acute antidepressive effects of lithium: 'this must be weak if it exists since this role has not been obviously recognised by groups with a long and wide experience of lithium treatment' (Hullin, 1978). In the face of these contradictory views it seemed to us that further controlled studies should be performed.

In the work supporting the efficacy of lithium as an acute antidepressant a number of factors have been claimed to be associated with a positive response: these include bipolar illness (Goodwin *et al*, 1972; Baron *et al*, 1975; and Mendels, 1976) and a high red cell:serum lithium ratio (Mendels and Frazer, 1973). Although the drug appears more likely to help bipolar than unipolar depression an unequivocal lithium response in some unipolar patients has been shown in the placebo substitution studies of Goodwin *et al*, 1972; Noyes *et al*, 1974; Baron *et al*, 1975; and Mendels, 1976. We therefore decided to include patients suffering from both unipolar and bipolar illness in our study. However, we thought it likely that patients with *recurrent* illness, whether unipolar or bipolar, would be a relatively more homogeneous sample of manic-depressive patients and more likely to respond to lithium than patients experiencing their first attack of affective illness. The two trials reported here were conducted on female in-patients in one research ward. In the first trial (Trial I–L) we compared the effects of lithium against imipramine and in the second trial (Trial T–L) we compared lithium and tryptophan (in the form of Optimax) against tryptophan alone.

Trial I-L

Method

A patient was admitted to the trial if she was between the ages of 40 and 75, gave valid consent and if two of the investigators agreed on the following: (1) that the patient fulfilled the criteria for depressive illness (Medical Research Council, 1965); (2) that the patient had had at least one previous episode of affective illness, either hypomania or depression, lasting at least one month; (3) that the patient had not received either lithium or a tricyclic antidepressant in adequate dosage for fourteen days within the previous three months.

As well as fulfilling the MRC criteria for depressive illness all patients were given the diagnosis of manic-depressive psychosis, depressed type, ICD 296.2 or manic-depressive psychosis, circular type, ICD 296.3. Prior to the start of the trial the majority of the patients were the subjects of biochemical research in a metabolic research unit and are representative of the patients considered to be manic-depressive in studies of erythrocyte membrane cation carrier published from Dundee (Naylor *et al*, 1973, 1976 and 1977). No patient was started on the trial without first spending seven days either in the metabolic unit or the research ward. During those seven days the only medication allowed was nitrazepam 10 mg at night and occasionally nitrazepam 5 mg up to three times per day if agitation was marked. Any patient who showed spontaneous clinically significant improvement during that time was not entered into the trial.

Medication was given for three weeks under double-blind conditions. Identical looking tablets containing lithium 300 mg, imipramine 25 mg or an inert substance had been provided by Pharmax Ltd. An investigation prior to the start of the trial had shown that the trial imipramine tablets and British National Formulary imipramine had the same bioavailability.

Patients were randomly allocated to receive either imipramine or lithium. Each patient was given seven tablets per day in divided dosage. For patients assigned to lithium the seven tablets consisted of lithium in dosage required to produce serum lithium levels between 0.8 and 1.2 mmol/l twelve hours after the last dose and placebo tablets added to make up the seven tablets. Patients receiving imipramine were given six imipramine tablets and one placebo. Based on an assessment of the patient's age, weight and serum creatinine a dose of lithium was given which was estimated to produce therapeutic levels in the first week of the trial. To maintain blindness medication was thereafter adjusted by withdrawing all tablets at the end of each week and adjusting lithium dosage based on plasma lithium levels taken on the 8th and 15th day of the trial.

A venous blood sample was taken from every patient on the morning of the 8th, 15th and 22nd day of the trial. For those patients receiving lithium the serum lithium was estimated by the method of Pybus and Bowers (1970), red cell lithium by a method described in a previous paper (Worrall *et al*, 1975) and the RBC:plasma lithium ratio calculated. For those patients receiving imipramine total plasma imipramine and desmethylimipramine was estimated using the method of Moody *et al* (1967).

One of the investigators scored items 1–16 of the Hamilton Rating Scale for Depression (Hamilton, 1967) for each patient on the morning of the 1st, 8th, 15th and 22nd days of the trial. Since nursing staff were independently rating the patients a departure was made from Hamilton's original recommendations for scoring: the clinicians rating the patients on the Hamilton scale did so solely on the patient's appearance and subjective reports and did not seek corroborative evidence from the nursing staff. All nursing staff in contact with the patients completed a seven-point global rating scale for depression during the appropriate nursing shift. These shifts were from 8 a.m. until 12-noon and from 12 noon until 8 p.m. For each patient all the nurses in each shift gave a rating on the depression scale. The median of these ratings was the patient's score for that shift and there were thus two scores per day. These scores were averaged over the week to give the mean weekly depression score.

Unipolar illness was defined as at least two previous episodes of depression, the patient never having been hypomanic. A history of hypomania whether or not this led to admission defined bipolar illness. Those patients with less

than two previous episodes of depression and who had never been hypomanic were considered to be of indeterminate polarity. Polarity was redetermined at the time of writing and classification corrected where necessary.

Thirty-two patients entered trial I–L. One patient on imipramine and one on lithium were withdrawn as their depression seriously worsened during the trial. A second lithium patient was withdrawn as she fell and fractured her femur. Of the 29 remaining patients, 14 received lithium and 15 imipramine. The mean age of both groups was not significantly different. Mean age ± SEM = 59.9 ± 2.9 years and 54.5 ± 2.5 years (t = 1.40). Both groups were comparable in polarity. The lithium group contained 7 unipolars, 5 bipolars and 2 who were indeterminate. The imipramine group comprised 10 unipolars, 3 bipolars and 2 indeterminate patients. There was no significant difference between the two groups in respect of the number of previous episodes of affective disorder; just over half in each group had fewer than four previous episodes.

Results

Fig 1 shows the mean Hamilton scores and nurse ratings for the 29 patients who completed the 22 days of trial I–L.

There was a significant difference between lithium and imipramine in the variances of the Hamilton scores at Day 22 although there was no such difference at Day 1. The variance of the imipramine group at Day 22 was 89.67 (n = 15) while that of the lithium group was 19.26 (n = 14) (F max = 4.66, P < 0.01, Kirk, 1968). This finding indicates that the outcome was more uniform for the lithium group, i.e. all patients in this group showed improvement whereas this was not so in the imipramine group.

Analysis of variance of the transformed Hamilton scores using a split-plot factorial ANOVA (Kirk, 1968) to evaluate differential changes over time showed a highly significant change in both drug groups over time (P < 0.005) and also a significant interaction between the drug groups and time of observation (P < 0.05). The nurse ratings showed the same trends with significant changes in the scores of both drug groups over time (P < 0.005) but on this measure the interaction was not significant.

The nature of the interaction between drug and Hamilton scores is suggested from inspection of Fig 1. There appears to be a difference between the two drugs in the time of maximal change of the scores. Paired t tests on the Hamilton scores (Table I) shows that in the imipramine group the mean Hamilton scores improved significantly between Days 1 and 8 and thereafter there was no significant improvement. The lithium group did not improve until the second week with significant changes in mean scores occurring between the 8th and 15th day and the 15th and 22nd day.

In summary, in this group of patients at the end of three weeks lithium produced sig-

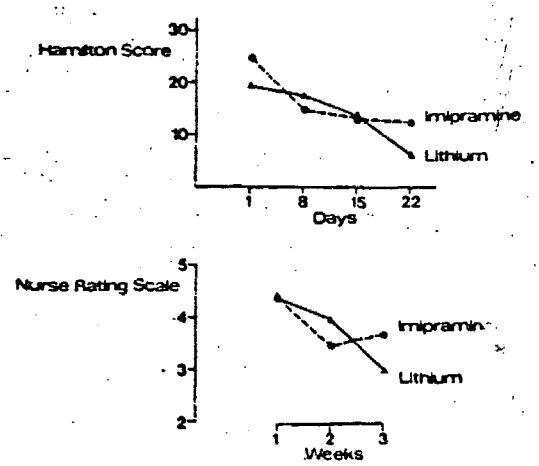

FIG 1.—Trial I–L. Mean Hamilton and nurse ratings.

TABLE I

Paired t-test. Difference in mean Hamilton scores. Significance levels

TRIAL I–L

Drug group	Days 1–8	8–15	15–22
Imipramine	< 0.01	NS	NS
Lithium	NS	P < 0.05	P < 0.001

nificantly more uniform improvement in Hamilton scores than did imipramine. Improvement on imipramine occurred during the first week of the trial whereas improvement in the lithium patients was not seen until the second and third week.

Trial T-L

Method

Since failure to respond to a tricyclic antidepressant is one of the reasons for deciding on in-patient treatment, many of the depressed patients who otherwise fulfilled the criteria had to be excluded from trial I–L. In these excluded patients we compared the effects of lithium and tryptophan (in the form of Optimax) and tryptophan alone. In this second trial we widened the criteria, included patients between the ages of 25 and 75 and did not specify that patients had to have had a previous episode of affective illness but excluded patients who had received either lithium and tryptophan together or tryptophan alone in the preceding three months. These patients were therefore potentially a more heterogeneous group than in trial I–L. As in trial I–L all patients had to fulfil the MRC criteria for depressive illness, all were given the diagnosis of manic-depressive psychosis, ICD 296.2 or 296.3 and no patient was started in the trial without first spending seven days either in the metabolic unit or the research ward. The form of ratings made and the times at which they were made were identical to trial I–L.

The patients were randomly assigned to receive either lithium and tryptophan or tryptophan alone. All patients received tryptophan 2 g three times per day. Those patients assigned to receive lithium were given lithium tablets in a dosage required to produce plasma lithium levels of 0.8 to 1.2 mmol/l. Those patients assigned to tryptophan alone received placebo lithium tablets. In this trial open dosage adjustments were made to lithium tablets at the end of the first and at the end of the second week of treatment, and random alterations were made to the dose of placebo tablets in order to preserve the blind conditions. A venous blood sample was taken from every patient on the morning of the 8th, 15th and 22nd day. Lithium estimations were made as described in trial I–L. Blood from those patients receiving tryptophan alone was discarded.

Thirty-one patients entered trial T–L, one patient receiving tryptophan alone was withdrawn as her condition worsened and one patient on lithium was withdrawn as she developed diarrhoea, probably a side effect of the drug. Of the 29 remaining patients 15 received lithium/tryptophan combination and 14 received tryptophan alone. The mean age for both groups was similar 55.8 ± 3.1 years and 53.6 ± 4.24 years ($t = 0.428$, NS). Polarity was also comparable. Seven of the combined drug group and 6 of the tryptophan only were unipolars, four of the combined drug group and one of the tryptophan only patients had bipolar illness and there were four indeterminate patients in the combined drug group and seven in the other. There was no significant difference in the two groups in respect of the number of previous episodes. At the time of writing for only six of the 29 patients has the trial illness been their only episode of affective disorder. Despite the widening of the criteria for this trial the majority of the patients therefore proved to suffer from recurrent affective disorder and were therefore, in this respect, comparable to the patients in trial I–L.

Results

Fig 2 shows the mean Hamilton and nurse

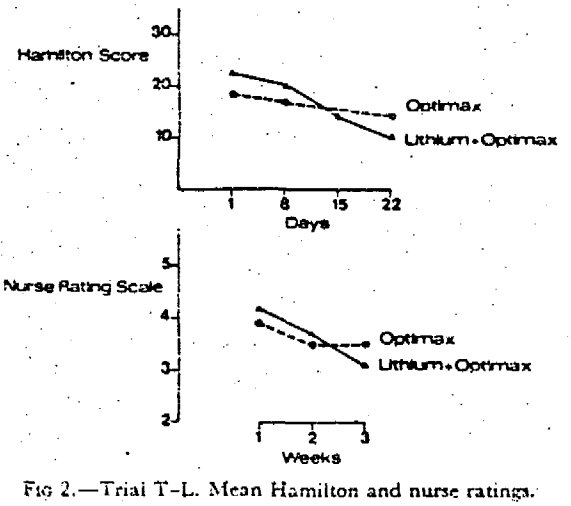

Fig 2.—Trial T–L. Mean Hamilton and nurse ratings.

ratings for the 29 patients who completed 22 days of trial T–L.

Analysis of variance of the Hamilton scores showed significant changes over time in the patients receiving combined drugs ($P < 0.005$) but no significant change in the group receiving tryptophan alone. There was a significant interaction between the two drug treatments and changes over time in HRS ($P < 0.01$). The nurse ratings again showed the same trends with equally significant changes in the patients receiving combined drugs but no change in the tryptophan only group. The drug-occasion interaction showed the same trend as with the Hamilton measure but was not significant ($P < 0.2$).

Exploring the time of change in the lithium group mean Hamilton scores by means of paired t tests showed that as in trial I–L the improvement only occurred between Days 8 and 15 and 15 and 22 (Table II).

TABLE II

Paired t-test. Difference in mean Hamilton scores. Significance levels

TRIAL T–L

Drug group	Days		
	1–8	8–15	15–22
Lithium + Optimax	NS	$P < 0.01$	$P < 0.01$

In summary, in this group of patients lithium and tryptophan in combination was clearly superior to tryptophan alone. The latter drug appeared to be devoid of any antidepressant activity. As in trial I–L the improvement in the combined drug group only occurred in the second and third weeks of treatment.

Drug Concentrations in Blood and Clinical Response

Lithium levels in the desired range were achieved for the majority of patients in the first week of both trials (mean ± SEM = 0.91 ± 0.11 and 0.85 ± 0.09 mmol/l). In trial I–L the lithium values for the last week of the trial were as follows: Plasma lithium = 0.93 ± 0.06 mmol/l, RBC lithium = 0.5 ± 0.05 mmol/l of red blood cells and RBC:plasma lithium ratio = 0.54 ± 0.04. In trial T–L the equivalent values were 0.86 ± 0.06 mmol/l, 0.48 ± 0.05 mmol/l of RBC's and 0.56 ± 0.03.

There was as to be expected a large range of steady state total plasma imipramine and desmethylimipramine levels. In the third week of the trial the mean value ± SEM was 404 ± 76 ng/ml with a range of 90 to 981 ng/ml.

There was no relationship between the percentage change in the Hamilton ratings over the 22 days and the lithium ratio at Day 22 either in the trials considered separately or together. Neither was there any obvious relationship between steady state tricyclic levels and percentage change in the Hamilton ratings.

The mean lithium ratio at Day 22 for all bipolar patients was 0.46 and for all unipolars was 0.58. This difference is statistically significant ($t = 2.15$, $df 21$, $P < .05$).

Discussion

The two trials reported here were conducted on female in-patients with recurrent affective disorder.

The trials suggest that in these patients lithium whether alone or in combination with tryptophan has clinically and statistically significant antidepressant effects and at the end of three weeks produces more uniform improvement than does imipramine. These findings should only be applied to male patients with caution. The Medical Research Council (1965) study suggested that female patients responded best to ECT whereas male patients improved more with imipramine. Nevertheless in clinical practice endogenously depressed female patients are usually offered antidepressant drug treatment. Given adequate supervision, in some of these patients lithium may be preferable to tricyclic antidepressants.

The high placebo response rate in endogenous depression tends to reduce the chances of finding significant differences between antidepressant drugs unless very large numbers of patients are used (Jenner, 1977). Such numbers of depressed patients are nowadays difficult to find (Little *et al*, 1978). In the present trials patients who showed improvement over the course of a week when given non-specific treatment were excluded from the two studies.

The lack of significant change in the group receiving tryptophan alone suggests that this policy was successful in reducing contamination from placebo effects and also that tryptophan in this sort of patient is ineffective. The design of trial T–L does not of course allow any inferences to be drawn as to whether tryptophan potentiates the antidepressant effects of lithium.

The time of onset of the antidepressant effects of lithium was consistent over both trials and over both sets of ratings. A significant effect was not seen until the second and third week of the trial. This time span is the same as that found with lithium's acute anti-manic effects (Peet, 1975) and its anti-aggressive effects (Worrall *et al*, 1975). The evidence from the placebo substitution studies of Goodwin *et al*, 1972; Noyes *et al*, 1975; Johnson, 1974; Baron *et al*, 1975 and Mendels, 1976; together with the group comparisons of Mendels *et al*, 1972; Watanabe *et al*, 1975; and the two trials reported here all lead to the conclusion that lithium has a major acute antidepressant effect. The European belief that the drug is devoid of useful acute antidepressant activity appears to be based on three early negative trials and early clinical experience of the drug. Hansen *et al* (quoted by Schou, 1968), Fieve *et al* (1968) and Stokes *et al* (1971) reported studies which failed to confirm any major antidepressant effects. The findings from these trials have been convincingly reinterpreted by Mendels (1976) as indicating a not proven or equivocal verdict rather than as definite evidence that the drug was relatively ineffective.

The contrast between the overall positive results from controlled trials and the poor opinion of the drug held by some European clinicians requires explanation. The three negative drug trials mentioned above were earlier than the positive trials and the early clinical experience of the major figures in the development of the prophylactic effects of lithium was unfavourable in regard to its antidepressant effects. It is possible that the sort of depressed patients now showing an antidepressant response are clinically different from the earlier patients. The studies reported here have shown that the antidepressant effects are not seen until the second and third weeks of treatment with adequate blood levels. The early negative study of Stokes *et al* (1971) looked at the effect after only ten days treatment. However, this cannot be a general explanation of the poor view held by early clinicians as few psychiatrists would give up looking for an antidepressant effect in an individual patient in less than three weeks treatment with an antidepressant drug. We suspect that early poor results have been uncritically accepted and not put to the test by later clinicians.

Our initial interest in the RBC:plasma lithium ratio in these patients arose out of the suggestion of Mendels and Frazer (1973) that this ratio was correlated with a positive antidepressant response. Later work by this group on a larger number of patients failed to replicate their earlier findings (Frazer *et al*, 1978). The lack of correlation in our study is in accord with the later work. The Philadelphia group (Frazer *et al*, 1978) and Cazullo *et al* (1975) have found higher mean lithium ratios in bipolar than in unipolar patients. This has not been a consistent finding by other workers (Lee and Paschalis, 1978). In the present study we found the opposite with unipolar patients having a higher mean lithium ratio than bipolar patients. It has been suggested that some of the discrepancies in this area may be partly explained by some investigators measuring the RBC lithium by the indirect method i.e. calculating the RBC value after measuring plasma and whole blood lithium (Frazer *et al*, 1977). Our results were obtained by directly measuring RBC lithium.

Although there is now reasonable agreement on the physiological factors determining the distribution of lithium across the RBC membrane (Ostrow *et al*, 1978; Griel and Eisenried, 1978; and Frazer *et al*, 1978) and on the influence of genetic factors on this distribution (Dorus *et al*, 1974; Ostrow *et al*, 1978; and Mendlewicz *et al*, 1978), useful clinical correlates of this information have still to be agreed.

Acknowledgements

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hypotension occurred in both groups, but more often and with greater severity in the clozapine group (average increase in pulse rate of 15 beats/minute). Although initially sedation was more apparent in clozapine treated patients, by the end of the study there was no difference between groups in this regard. Hypersalivation, especially at night, occurred more often with clozapine (11 of 13 patients *vs* 1 of 12 patients **'A review of the available reports shows that there is large concurrence that the antipsychotic effect of clozapine is at least equal to, and often greater than, comparable effects with other drugs of the phenothiazine or butyrophenone class of antipsychotic agents.'**

Shopsin, B. et al.: Archives of General Psychiatry 36: 657 (June 1979)

And lithium: a controlled trial shows positive results

The effects of lithium in 13 psychotic schizophrenic patients were investigated in a placebo controlled, double-blind study. Patients took a placebo for at least 1 week prior to 3 weeks of lithium therapy and for 2 weeks after.

Lithium carbonate was administered in a dose of 1800mg for 3 days followed by a lowering of the dose to a suitable maintenance level. The average dose during the third week was 1600mg daily and the average serum level was 0.9mEq/L (range 0.7-1.2mEq/L). Seven of 13 patients showed clinical improvement during the third week on lithium; 4 of these 7 responders relapsed within 2 weeks of lithium withdrawal. When psychosis ratings of responders and non-responsers were compared, the mean ratings of the 2 groups did not differ significantly during the first placebo period, but the improvement in the responders became apparent during the first week of lithium administration, and this was the only predictive factor of response observed. The overall extent of improvement was modest, with no patients showing a complete disappearance of psychotic symptoms.

'The findings suggest that the clinical efficacy of lithium is not disease-specific for manic-depressive illness, as others have suggested . . . Further controlled clinical trials of lithium in the treatment of schizophrenia are indicated.'

Alexander, P.E. et al.: American Journal of Psychiatry 136: 283 (Mar 1979)

VERAPAMIL IS EFFECTIVE IN HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

And, indeed, may be superior to β-blockers

β-Blockers, especially propranolol, have been used for more than 10 years in the treatment of hypertrophic obstructive cardiomyopathy (HOCM) but long term follow-up casts considerable doubt on their effectiveness. Recently the calcium inhibitor, verapamil, administered in a mean oral dose of 480mg daily, was found to treat HOCM adequately in 22 patients. After an average of 15 months of treatment, the QRS amplitude in the ECG was significantly reduced from 4.2 to 3.8mV and heart volume also decreased significantly. Coronary artery diameter decreased in 7 patients, increased in 1, and was unchanged in 2. In 10 patients, follow-up heart catheterisation showed a decrease in left ventricular muscle mass in 7 patients and a slight increase in 3 patients. The reduction in coronary diameter is considered to be a consequence of a reduced heart muscle mass. The investigators concluded from this data that verapamil therapy is superior to β-blockers in the treatment of HOCM.

Kaltenbech, M. et al.: British Heart Journal 42: 35 (Jul 1979)

PROPRANOLOL FOR ACUTE INTERMITTENT PORPHYRIA

It may prove preferable to many other treatments tried

Propranolol in doses ranging from 20-200mg was given to 20 patients with acute intermittent porphyria. It adequately controlled tachycardia in all patients and hypertension in 17. All cases had been given a course of promazine (before propranolol therapy) which produced symptomatic relief but had no effect on pulse rate and BP. **'Propranolol did not enhance the rate of alleviation of symptoms such as abdominal pain, nausea, vomiting and constipation, but the general condition of the patient improved visibly from the first week of therapy.'** Patients taking 200mg of propranolol daily complained of occasional fatigue and giddiness. At follow-up, smaller propranolol doses were found to maintain the pulse rate and blood pressure within normal limits and also to prevent acute attacks.

Menawat, A.S. et al.: Postgraduate Medical Journal 55: 546 (Aug 1979)

CEFOXITIN THERAPY EVALUATED IN CHILDREN

Cefoxitin 80 to 160mg/kg daily was evaluated for safety and efficacy in 26 children (aged 3 months to 7 years) in the treatment of cellulitis (13 patients), pneumonia (5 patients), and bone and joint infection (4 patients). Nine patients were bacteraemic. *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae* were the most frequent pathogens recovered, and were very susceptible to cefoxitin. All 26 children were considered improved or cured, no severe adverse reactions being encountered. Eosinophilia (12%), phlebitis (4%), and elevated liver function tests (4%) were associated with therapy.

Jacobson, J.A. et al.: Antimicrobial Agents and Chemotherapy 16: 183 (Aug 1979)

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outlook in many forms of cancer could be improved substantially if new treatments, and modifications to existing ones, were guided by the sort of clinical feedback provided in the acute lymphoblastic leukæmia trials.

The survey reported on p. 623 therefore makes cheerless reading. Apart from those with leukæmia or lymphoma, fewer than 10% of all cancer patients in the U.K. are included in any form of randomised clinical trial. Most of the studies are on a small scale and there is rarely any coordination between individual trials involving the same categories of patient. This state of affairs cannot be taken to reflect satisfaction with existing therapy. In the case of lung cancer, for example, only about 1% of all patients are included in clinical trials despite universal recognition of the need for better forms of treatment. Nor can it reasonably be attributed to reluctance on the part of physicians and surgeons to cooperate in such trials—unless the supposition is that those who care for children with acute leukæmia are a very different breed from those who look after patients with other forms of cancer.

During the past decade, important decisions have been reached about the future of clinical oncology services in the U.K. The Department of Health, acting on advice from many learned quarters, has encouraged the establishment of academic units whose functions include the provision of specialist training, the fostering of research, the raising of standards of cancer treatment by precept and example, and the organisation of clinical trials.[6,7] Of those units now functioning, most are new university departments with small staffs and inadequate budgets, battling in these unpropitious times for beds, for laboratory space, and for research funds. It is unrealistic to expect them to initiate and supervise clinical trials of common cancers on a national scale. In 1973, the Cancer Coordinating Committee, drawn from the Medical Research Council, the Cancer Research Campaign, and the Imperial Cancer Research Fund, recommended that 60 new career and training posts should be established in clinical oncology. In addition to university chairs, N.H.S. consultancies, and the like, they suggested that there should be "four or five staff to coordinate multicentre trials".[8] With this miserable level of commitment, who can be surprised by the absence of national cancer trials in the U.K.? Yet the structure of the National Health Service offers scope for clinical trials on a scale which most countries could not hope to undertake and which the Cancer Coordinating Committee clearly has not begun to contemplate.

The near-uniformity of standards and of practice throughout the U.K., the integration of academic centres within the Health Service, and the absence of direct financial dealings between doctor and patient combine to provide a setting which comes close to the ideal for multicentre cooperative trials. We could and should be improving the application of existing treatments for both rare and common cancers by comparing a range of dose and time schedules and testing different combinations of drugs and radiotherapy. If national multicentre trials were the norm rather than the rare exception, we should have the means for prompt assessment of promising new modes of treatment. Basic research into the causes and nature of cancer would not be hampered; nor need there be any infringement of the role of specialist oncology centres. Miss TATE and her colleagues have exposed a situation which can only be termed a disgrace.

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LITHIUM NEPHROPATHY

THE most common renal effect of lithium salts is an initial sodium diuresis, lasting a few days,[1] followed by a few weeks of mild polyuria and polydipsia. About 10% of patients have impairment of renal concentrating ability which may persist or recur unpredictably after months or years.[2] The polyuria rarely exceeds 3 litres a day and is usually regarded as harmless and reversible by withdrawal of the drug.[3] Occasionally, however, frank nephrogenic diabetes insipidus ensues which may be irreversible.[4] The mechanism has yet to be fully defined. Lithium shares many physical and chemical properties with sodium and potassium (periodic table, group 1). Apart from its effect on electrolyte balance across cell membranes, it enters cells freely where it may alter the microenvironment necessary for the proper action of hormones.[5] In the cells of the distal tubule and collecting duct, antidiuretic hormone increases permeability to water by activating adenyl cyclase to produce cyclic AMP. Lithium probably interferes with the action of activated adenyl cyclase and cyclic AMP, leading to diabetes insipidus.[6,7] Surprisingly, there have been few reports of renal tubular damage in animals exposed to

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lithium and most of these are difficult to interpret because toxic doses were used. Epithelial degeneration and dilatation of the distal part of the nephron have been induced in dogs,[8] as have degenerative changes in the proximal tubules of rats.[9] Ultrastructural lesions have been noted in lithium-treated rats with blood-levels corresponding to the therapeutic range in man.[10] Initially there are mitochondrial changes with bulging of the cytoplasm of tubular cells, then follow liquefaction, karyolysis, and karyorrhexis of the distal tubule and collecting duct.

Isolated cases of renal failure associated with severe lithium intoxication have been reported in man,[11-13] but neither acute nor chronic uræmia should arise in a patient whose treatment is well controlled. In 1977, Hestbech and co-workers[16] reported chronic renal lesions in 13 patients who had been treated with lithium for 1½ to 14 years. In 8 of them the lithium intoxication was acute, and the other 5 had severe polyuria. The lesions were non-specific, consisting of nephron atrophy and focal interstitial fibrosis. Although the same changes were seen in age-matched controls, there was a significant increase in totally sclerotic glomeruli, tubular atrophy, and the amount of interstitial fibrous tissue. Kincaid-Smith[17] also described tubular lesions in 5 patients who had been on lithium from 4 months to 9 years. None of her patients had lithium intoxication, yet she found "unique" lesions in 2 patients who had received lithium for only 4 and 5 months. In the other 3 patients, who had taken lithium for several years, the changes were more advanced and were akin to those in Hestbech's group. She concluded that the pathological changes increased with prolonged lithium treatment; yet, interestingly, despite the impressive morphological features, the serum-creatinine was normal and the urine was clear of protein and red cells.

These reports have stimulated several studies of renal function in patients on long-term lithium. So far opinions differ. Cattell[18] confirmed mild polyuria in about a third of 79 patients on lithium carbonate (a side-effect he regarded as acceptable), whereas Bucht and Wahlin[19] found impaired renal concentration in the majority of their 60 patients which was still present 2 months after withdrawal of lithium. The defect was proportional to the total quantity of lithium consumed.

Hallgren et al.[20] have lately studied renal function in 66 patients on lithium treatment. 9 had slightly subnormal renal function, although the defect could have been present before lithium was started anything from 1 to 15 years earlier. 4 of these patients had a slightly depressed glomerular filtration-rate (measured by ^{51}Cr EDTA clearance), 3 had mild albuminuria, and 2 had so-called tubular proteinuria (increased β_2-microglobulin excretion). Renal biopsies were not done. Hällgren and co-workers suggest that lithium cannot be exonerated and recommend regular testing of glomerular filtration-rate and of albumin and β_2 microglobulin excretion in patients on lithium. This seems rather a tall order for psychiatrists dealing with manic-depressive patients, and on existing evidence the advice seems ill-founded. The incidence of nephropathy in Hällgren's patients is small and the relation to lithium by no means proven.

Lithium has a narrow margin of safety, so patients must have their blood-levels checked regularly. To a brief inquiry about polyuria, measurement of the serum-creatinine should perhaps be added, with a check for proteinuria. The meaning of the pathological and functional abnormalities in the renal tubule remains to be seen. Are they related? Do they matter? Lithium is a valuable drug in the management of manic depressive disorders, so any long-term hazard must be clearly defined so that the drawbacks can be properly weighed against the benefits.

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FORMALDEHYDE TOXICITY

INHALATION of the fume of formaldehyde is a cause of asthma and bronchitis[1] and everyone in the industrialised nations is exposed to it, at least transiently. It is present in the exhaust from petrol and diesel engines and in tobacco smoke. Several thermosetting plastics are formed by the condensation of phenol, cresol, or melamine formaldehyde. Urea formaldehyde is used in the manufacture of chipboard and hardboard, as a constituent of cavity-wall insulation, and in the production of permanent-pressed garments. Formalin is a disinfectant and an embalming fluid. Very little is known about the mechanism by which low-level exposure to formaldehyde causes respiratory disease. Next to nothing is known about the prevalence of formaldehyde-induced lung disease and about exposure levels at the workplace.

Harris[1] reported that, of 23 workers in a plastics factory using urea formaldehyde, 4 had work-related respiratory disease. Schoenberg and Mitchell[2] investigated 63 workers on a production line using phenol formaldehyde, with basic spirometric tests and symptom scores by questionnaire.[3] Workers were divided into four exposure groups according to how many years they had been on the line and were compared with an unexposed group. The prevalence of wheeze, chest tightness, and

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Potentiation of Lithium by Tryptophan in a Patient with Bipolar Illness

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The results of our recent double-blind controlled study of the action of tryptophan and imipramine in the treatment of newly admitted depressed patients led us to hypothesize that unipolar and bipolar patients differ in their response to tryptophan (1, 2). Bipolar patients and patients with acute mania seem to require higher doses of tryptophan than do unipolar patients. Two studies of acute manic patients showed moderate (3) or no (4) therapeutic effect with 6 g of tryptophan a day, but a third study achieved better results using an average dose of 9.6 g/day (5). In an unpublished pilot study we have obtained encouraging results from the use of 12 g/day of tryptophan in manic patients. If high doses of tryptophan are therapeutic in both manic and bipolar depressed patients, this drug might be useful in manic-depressive illness, especially for patients who do not respond satisfactorily to lithium. This paper is, to our knowledge, the first report of potentiation of lithium by tryptophan in a patient who responded poorly to lithium.

Case Report

Ms. A, a 46-year-old married woman, had no psychiatric history and was working successfully in an executive position when she experienced her first depressive episode at age 42. The episode was characterized by lack of energy, suicidal ideation, insomnia, weight loss, guilt feelings, and feelings of helplessness. These symptoms responded to amitriptyline, 50 mg p.o. b.i.d., but Ms. A stopped the medication because she became overactive and hostile, exhibited pressure of speech, and began spending inappropriate sums of money. Approximately 1 month after she stopped taking the antidepressant, she became extremely depressed and was admitted to the hospital with suicidal ideation. In the hospital she responded well to tricyclic antidepressants and was discharged, but 6 weeks later her hypomanic symptoms reappeared. Although the medication was continued, her depressive symptoms returned within 1 month and she was readmitted after she attempted suicide by overdose. She was given antidepressants, recovered, and was discharged.

At this point, Ms. A started a cyclic pattern of mood changes that usually consisted of a 2-week period of mania or hypomania, 2-3 days of normal mood, and then 2 weeks of depression (the depressed phase lasted up to 2 months at times). This cycle did not correspond to her menstrual cycle. During the depressed phase Ms. A was unable to do anything beyond the most basic necessities of caring for herself, and she spent most of her time in bed. It was necessary to discontinue antidepressants because they precipitated more severe manic periods and did not prevent the depressed phase.

At the age of 44, Ms. A was readmitted to the hospital in an attempt to stabilize her on lithium. Lithium carbonate, 300 mg p.o. q.i.d., lessened the severity of the manic phase, but the time course of the cycle remained unchanged. Approximately 3 months after she was discharged, perphenazine, 4 mg/day, was added to lessen the subjective anxiety that she experienced during both depressed and manic phases. Throughout the next year and a half, Ms. A continued to experience the cycle of depressive and manic periods and was unable to work despite serum lithium levels of approximately 1 mEq/liter. She lived with friends who cared for her during the recurrent depressed phases and prevented her from acting on her severe suicidal ideation.

Ms. A was referred to our pharmacology research unit for consultation concerning possible change in the treatment regimen, which consisted then of lithium carbonate, 300 mg p.o. q.i.d.; perphenazine, 4 mg/day p.o.; and flurazepam, 30 mg q.h.s. as needed for insomnia. Her medical history included a male first cousin on her father's side who had a history of bipolar affective illness. Physical examination and routine laboratory analysis were normal. There was no history of drug abuse or alcoholism.

It was decided to add L-tryptophan, 3 g p.o. b.i.d., and nicotinamide, 750 mg p.o. b.i.d., to her treatment regimen. Informed written consent was obtained from the patient. Nicotinamide was given with tryptophan in order to decrease the peripheral catabolism of tryptophan by tryptophan pyrrolase (6). She was rated on the Hamilton Rating Scale for Depression, the Beck Self-Rating Inventory for Depression, and a 5-item mania scale before treatment and at weekly intervals thereafter. At the same time intervals, blood was drawn for the measurement of plasma tryptophan and serum lithium. An ultrafiltrate of plasma, prepared as described previously (2), was used for the measurement of free (non-albumin-bound) plasma tryptophan. Tryptophan was measured by the method of Denckla and Dewey (7). On day 30 of the trial, the dosage was increased to 3 g q.i.d. of L-tryptophan and 1 g q.i.d. of nicotinamide. She tolerated this high dose very well. During the 8th week she discontinued flurazepam because her sleep had improved and at week 10 a marked reduction in anxiety enabled her to stop the perphenazine. She continued throughout the trial on lithium carbonate, 300 mg p.o. q.i.d.

Table 1 shows the results of all evaluations. It can be seen that during the study period Ms. A exhibited 2 complete cycles, the first ending on week 3 and the second ending on week 8. The depressed phase of cycle 2 was reduced in intensity on both the Beck and Hamilton scales as compared with the first cycle. The third cycle started on week 9 with a manic phase of slightly reduced intensity, but on week 10, when the patient's plasma tryptophan levels were higher than any level reached previously, she was considered by

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TABLE 1
Weekly Measurements of Psychopathology, Plasma Tryptophan, and Serum Lithium

Week	Hamilton Depression Scale*	Beck Inventory	Mania Scale*	Plasma Tryptophan (mg/ml) Total	Plasma Tryptophan (mg/ml) Free	Serum Lithium (mEq/liter)
0	5	4	8	9.4	2.3	1.17
1	3	3	2	12.9	3.2	0.86
2	39	41	0	32.7	10.4	1.00
3	37	42	0	67.6	21.8	0.89
4	4	5	8	22.9	9.0	0.91
5	3	3	4	98.4	24.4	1.17
6	3	3	4	19.8	4.1	0.87
7	30	33	0	16.4	3.8	0.95
8	22	36	0	76.7	23.5	1.00
9	2	3	6	31.0	7.8	0.96
10	2	3	0	110.8	51.6	0.87
11	2	3	0	104.2	36.0	0.91
12	2	3	0	52.7	10.4	0.96
13	4	3	0	142.0	63.2	0.39
14	2	3	0	137.0	47.6	0.87

*Total scores.

both herself and two psychiatrists to be normal. At the time of writing she has remained normal for sixteen weeks. The only item on both the Beck and Hamilton scales that remains elevated is sexual dysfunction, consisting of a loss of libido. The patient has not yet resumed her normal sex life.

Discussion

Although lithium is usually an efficacious treatment for bipolar affective illness, there remains a small percentage of patients who do not respond satisfactorily. Incomplete responders to lithium therapy are often given additional medications such as neuroleptics or tricyclic antidepressants, but such drug combinations have met with little success. In the case described here, the patient had been treated with tricyclics, lithium alone, and subsequently with lithium in combination with a neuroleptic. These treatment regimens had not adequately controlled her manic or depressive symptoms or altered the cycle's length. However, the addition of tryptophan-nicotinamide to lithium resulted in an almost complete remission of symptoms. The first effect was seen 7 weeks after addition of tryptophan-nicotinamide, with a reduction in the severity of the depressed phase. After 10 weeks the patient entered her first extended period of normality since the illness began 4 years ago.

Lithium reduced the severity of both manic and depressed episodes, but the cycle itself continued. The addition of tryptophan-nicotinamide resulted in a further reduction in the severity of symptoms and a return to normality. However, we have clinical and biochemical evidence from studies in progress which indicates that the cycle continues but does not induce symptoms in the patient. For example, Ms. A reports greater difficulty in sleeping at the time of the expected switchover. This suggests that tryptophan acts in a similar way to lithium and raises the question of whether tryptophan potentiates the action of lithium or has a therapeutic effect of its own. Whatever tryptophan's mode of action, this case is consistent with our hypothesis (1, 2) that only high doses of tryptophan are of therapeutic value in bipolar illness, whereas lower doses are required in unipolar illness. The fact that tryptophan may have some antimanic action in acute mania when given at high doses (unpublished data) also supports the idea that tryptophan when given in combination with lithium may be an effective and nontoxic prophylactic agent for use in manic-depressive illness.

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BIOEQUIVALENCE OF LITHIUM PREPARATIONS

There are five lithium preparations with psychotropic indications which are the subject of Product Licences.
Certain hospitals also manufacture liquid preparations of lithium for oral administration.
The British Pharmacopoeia contains two monographs on lithium preparations - Lithium Carbonate Tablets, and Slow Lithium Carbonate Tablets. At present there is no dissolution specification for the Lithium Carbonate Tablets BP, but this is under consideration by the BP Commission, as is a revision of the dissolution requirements for the Slow Tablets.

A new product licence application for a "controlled release" lithium carbonate tablet (Liskonium - PL/0002/0083) was considered by the Committee on Safety of Medicines in September 1979. They are minded to recommend rejection of the application, as they are not satisfied about the release characteristics, and consider there could be a safety hazard.
When the Sub-Committee on Chemistry Pharmacy and Standards considered the application, they recommended that steps should be taken to standardise all sustained release marketed products containing lithium carbonate to a single specification.

When the Committee on Review of Medicines considered lithium carbonate tablets in 1978, it was recommended that the dissolution pattern for each preparation be specified.

Inspection of the tests currently in use shows there is wide variation in conditions. This extends to the apparatus, the speed of rotation, the number of tablets used, temperature range, the dissolution fluids, and the measurement times.

It is also claimed that in vitro disintegration equivalence gives no assurance of bioequivalence.

RECOMMENDATION

- [redacted]
- [redacted]
- [redacted]

A T Gray
2/10/79

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COMMITTEE ON REVIEW OF MEDICINES

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

PHARMACEUTICAL RECOMMENDATION

LITHIUM CARBONATE

[redacted]

Legal Status

Lithium Carbonate is available on prescription only except where the maximum dose is the equivalent of 5mg of the base or less and the maximum daily dose is 15mg of the base or less.

NOT FOR PUBLICATION COMMITTEE ON THE REVIEW OF MEDICINES

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

Ingredient No: A 1926

Date of Meeting: October 1978

Medical Assessment: [redacted]

Pharmaceutical Assessment: [redacted]

REPORT ON LITHIUM CARBONATE

1. INTRODUCTION

1.1 Formula

$Li_2 CO_3$

Lithium Carbonate

1.2 Description

A white, crystalline powder; odourless; taste, slightly alkaline.

1.3 Background

Lithium was discovered in 1817 and named after the stone from which it was extracted ("lithos" - Greek). It occurs in many minerals, plant and human tissues although no biochemical or physioligical system is shown to need it.

It was a popular remedy in the 1850's for gout, renal calculi and rheumatism, and in the 1920's as an epileptic, a tonic and hypnotic. In the 1940's, Lithium chloride was introduced as a salt substitute but was withdrawn after toxicity cases were reported, especially in those with heart or kidney disease.

The efficacy of Lithium carbonate in mania was first discovered in 1949, and confirmed only in 1968.

1.4 Pharmacopoeal Entries

Lithium carbonate BP., also FR, Swiss and USP.

Lithium carbonate BP., also USP.

Slow Lithium carbonate tables BP.

Lithium carbonate capsules USP.

1.5 Pharmacopoeal Dose

Up to 1.6g daily, in single or divided doses; subsequent doses in accordance with the plasma concentration of lithium.

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1.6 Pharmacopoeal Indications

Used in theprophylaxis and treatment of manic-depressive disorders.

1.7 Legal Status

Lithium carbonate is avilable on prescription only.

An amendment to the Medicines (Prescription only) Order 1977 (SI 1977 No 2127) has been agreed in respect of Lithium carbonate ie products containing Lithium carbonate will be exempt from the class of prescription only medicines where the maximum dose is the equivalent of 5 mg of base or less and the maximum daily dose is 15 mg of base or less. (cf Lithium sulphate).

Products on the UK Market

There are 12 products on the UK market containing lithium carbonate, 5 of these, detailed below, contain lithium carbonate as the only active ingredient and are all promoted for use in the prophylaxis and treatment of manic-depressive disorders.

PL 0108/0055 (Pharmax)	Phasal tablets	300mg	Sustained release
PL 0332/0015	Camcolit 400 tablets	400mg	
PL 0332/5900 (Norgine)	Camcolit 250 tablets	250mg	
PL 0357/5000 (Delandale Labs)	Priadel tablets	400mg	Sustained release
PRL 0912/5892 (Woodward)	Lithium carbonate tablets BP	250mg	

The remaining 7 products contain smaller quanitites of lithium carbonate in combination with several other ingredients.

PLR 711/5005	Gout Varalettes	62.4mg Li_2CO_3 /unit dose
PLR 209/5006	Diuromil	0.39% Li_2CO_3 (cancelled)
PLR 711/5003	Granular Effervescent Citrate of Lithia	3.162% Li_2CO_3
PLR 711/5006	Urobishop	0.3% Li_2CO_3
PLR 711/5008	Carlsbad Salt	0.37% Li_2CO_3
PLR 2269/5007	Rehabiliation Bath AHP	1.2% Li_2CO_3
PLR 2269/5010	Bromine-Valerian Bath AHP	level of Li_2CO_3 not stated.

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PHARMACEUTICAL REPORT ON LITHIUM CARBONATE

Only the five products promoted as psychotropics are discussed.

Background

A specification for Lithium carbonate was included in the BPC 1949; a psychotropic use was not listed. The dose was 0.12-0.3g.

Lithium carbonate for use in the prophylaxis and treatment of manic-depressive disorders at a dose of up to 1.6g daily, first appeared in the BP addendum 1969. The BPmonograph was developed in consultation with Camden Chemical Co. Ltd.

[redacted]

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[redacted]

Bioavailability

The pharmacokinetics of Lithium are most easily related to partial ion substitution. Lithium salts are efficiently absorbed from the gastro-intestinal tract with peak and plateau serum concentrations in 30 minutes and 12-14 respectively (7). However, Lithium crosses cell boundaries at a relatively slow rate with a distribution volume equal to body water. This slow entry into and exit from

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the intracellular space accounts for the delay of 6-10 days in achieving the full therapeutic response to Lithium and for the delay in excretion when Lithium is discontinued.

The proprietary preparations contain different amounts of Lithium carbonate and recommend different dosage regimens (see Appendix II).

Preparations containing Lithium carbonate do not appear to be bioequivalent. This problem of the bioavailability of lithium from formulations containing Lithium carbonate has been widely reported and discussed. This has publicised the problem but nothing has, as yet, been done to resolve it.

In vivo studies showed that after a single dose of Camcolit (400), Priadel and Phasal similar plasma levels were found after Priadel and Camcolit but lower and more variable levels after Phasal (8). There appears to be a tendency for slightly lower serum levels on Phasal which might require a slight increase in dosage.

The interchangeability of Priadel and Camcolit 400 when Camcolit 400 was substituted in patients who were already stabilised on Priadel has been demonstrated. (In house data).

Camcolit 400 appears to be bioequivalent to Priadel.

Whilst both 'Phasal' and 'Priadel' claim slow release characteristics they are not generally reported to be bioequivalent. Apparent bioequivalence of the two products in a small trial of 18 schizophrenic patients is reported (9). Doses were given once daily at 7.0pm or 8.0am. 'Priadel' tended to give a higher peak in serum concentration of Lithium than 'Phasal' in the early period after drug administration. When the preparations were taken at night the serum concentrations of Lithium were not significantly different in the main waking hours of the day up to and including 6.0pm. The two preparations appeared to be bioequivalent in this study. For a once-a-day administration it is better to give sustained release forms of Lithium salts at night so that any peaks in serum concentration occur during sleep, but twice-a-day dosage is preferable.

Other studies have shown that 'Phasal' gives serum levels of 0.72 ± 0.02 m eq/l in stabilised subjects. (Unpublised results).

Plasma levels were compared in healthy volunteers after taking 'Camcolit' 400 or 'Camcolit' 250. Peak plasma levels after 'Camcolit' 400 were generally lower than after Camcolit 250. (In-house data). Whilst the company do not claim Camcolit 400 as a slow release preparation it is formulated in such a way that the release is controlled or optimised in order to avoid dangerously high peak levels when used by those physicians who prefer to give Lithium on a once daily dosage regimen.

In an, as yet unpublished investigation, Camcolit 250 was used in a once daily dosage regimen. Plasma levels over 24h were very variable therefore once daily dosage with Camcolit 250 is not recommended.

Some control over the release of Lithium carbonate seems to have been achieved with Camcolit 400.

Dosage of Lithium must be adjusted in the individual patient according to clinical conditions and the results of regular serum lithium determinations (range 0.6-1.5m Eq/l : not to exceed 2m Eq/l) therefore bioequivalence of products is important.

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Comment

[redacted]

3. Companies should be asked whether they would allow information on the five products specified to be exchanged between the CRM Secretariat and the BP Commission.

4. In Lithium carbonate therapy serum drug levels are done routinely. It is possible that the complete lack of uniformity of the products containing Lithium carbonate is a contributory factor to this requirement.

5. The CRM should be asked whether the non-uniformity of the products, the variable dissolution patterns and bioinequivalence constitute a possible clinical hazard.?

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Prescribing figures for products containing Lithium Carbonate

The data have been extracted from a statistical analysis of all prescriptions in Great Britain in 1976

Prescribing name	Number of prescriptions (thousands)	Type of prescription
Priadel (400 mg)	94.2	Proprietary
Phasal (300 mg)	2.8	"
Camcolit 250	16.1	"
Lithium carbonate 400mg	6.6	Non-proprietary
Lithium carbonate 300mg	0.2	(Prescriptions generic but only available as a proprietary)
Lithium carbonate 250mg	28.3	

Comments

1. Figures for Camcolit 400 are not included as the licence for this product was only granted 2.3.77.

2. Generic prescriptions do not appear to specify slow release characteristics for a product. The products must therefore be identified by tablet strength only.

3. Slow Lithium Carbonate tablets BP do not appear to be prescribed as such.

Appendix I

Comparison of specifications for Lithium Carbonate

[redacted]

APPENDIX II

Comparison of dosage and dissolution characteristics of products containing Lithium carbonate.

[redacted]

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CRM/003/79/25

NOT FOR PUBLICATION

COMMITTEE ON THE REVIEW OF MEDICINES

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

LITHIUM

1. Background

An ingredient report on lithium, together with suggested data sheet guideline recommendations, were seen by the Committee in October 1978 (Annex 1). At this time several reports of nephrotoxicity, including irreversible histological changes in the kidney, had just appeared in patients receiving long term lithium therapy (Annex 1, pp.7/8). The Committee, therefore, deferred their recommendations on the use of lithium in psychiatric disorders until results of known ongoing trials, which assessed renal function, were completed. Several further reports are now to hand and are summarized in this report.

2. New Data

i. Hestbech J et al, Lancet, Jan 27 1979, 212 (Annex 2)

Report possibly the first case of renal failure occurring in a patient following 3 years of lithium therapy. Blood levels (with one exception) had been maintained below 1.1 m mol. Renal function stabilised following withdrawal of lithium therapy. Renal biopsy showed focal interstitial cortical fibrosis and nephrotic atrophy.

ii. Mullin et al. BMJ, 2 June 1979, 1457-9 (Annex 3)

These authors investigated renal function in 106 patients attending a lithium clinic. They found the incidence of polyuria to be only 5.7% (compared with a 30% + incidence in previous reports) and a raised plasma creatinine was seen in approximately 5.5%. Creatinine clearance was reduced to below 50 ml/minute in approximately 15%. They suggested that the lower incidence of abnormal renal function in this series was due to the lower dose of lithium used. The average plasma lithium concentrations were maintained at 0.59 mmol/l (0.41 mg/100 ml) by a mean dose of 802 mg of lithium carbonate per day. In general, plasma levels are maintained at nearly twice this value. It is of significance that no increase in the relapse rate was observed by the present authors until plasma levels fell to below 0.4 mmol/l.

iii. B B Johnston et al, Brit J Psychiatry 134, 482, May 1979

Measured plasma and erythrocyte lithium concentrations in 49 manic depressives on routine lithium maintenance therapy. They found side effects in two-thirds (31) patients, which consisted mainly of tremors, or thirst, polydypsia-polyuria syndrome. Surprisingly, patients with side effects had significantly lower erythrocyte and plasma concentrations (0.394 and 0.787 mmol/l respectively than did those without side effects (levels = 0.56 and 0.93 mmol/l respectively). The erythrocyte/plasma ratio was 0.5 in the side effect group and 0.617 in the other.

iv. Other recent reports include:

a. A case of lithium poisoning which resulted in permanent neurologic, cardiac and hepatic damage following an intake of 2,700 mg/day for 10 days. Serum lithium reached 7.6 meg/l. Sequlae at 1 month following this episode of acute intoxication, included cerebellar and upper motor neurone symptoms, myocardial infarction and liver damage. (L H Warwick, The Western J. of Med. March 1979, 130, 3).

b. A report by J L Frolich et al (BMJ, 28 April 1979, 1115) showed a 59% increase in plasma lithium following concurrent medication with indomethacin, due to a reduction in lithium renal clearance (Annex 4).

c. A second report on the interaction of lithium and tetracycline (Annex 5) which describes a dramatic increase in serum lithium levels with signs of lithium toxicity 2-4 days after receiving tetracycline for a vaginal discharge.

v. A recent review on the renal toxicity of lithium published by the Drugs & Therapeutic Bulletin, V.17, 30 May 1979 (p.27/28) which also includes recommendations for use, is appended (Annex 6).

Medical Comment

The present state of knowledge regarding the effect of lithium on the kidney might be summarized as follows:-

Facts Established

a. Polyuria and polydypsia occurs in up to 40% of patients receiving long-term lithium therapy, probably due to antidiuretic hormone unresponsive diabetes insipidus.

b. Renal impairment/failure occurs in patients during acute lithium toxicity. Symptoms of failure including proteinuria, raised blood urea, oliguria etc. are usually reversible.

c. Permanent histological changes have been described in the kidney of patients following an episode of acute chronic lithium toxicity. In these patients, the impaired concentrating ability appears to correlate with the degree of histological involvement.

d. Histological changes have been observed (including "unique tubular lesion") in patients with no renal symptoms and normal renal function.

e. To date, the incidence of chronic renal failure - in patients receiving long-term lithium therapy is very low.

f. Plasma levels of lithium appear to relate, during chronic administration, to the symptoms of polyuria/polydypsia, and to the degree of renal failure and subsequent histological change, following acute intoxication.

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Facts Unknown

a. The significance of the symptoms polyuria and polydypsia in terms of subsequent renal function and/or histological change, i.e. do they occur independently or are they the beginning of a process ending in nephrotoxicity/failure.

b. Relation between histological changes and impaired renal function.

c. Timescale involved if the common urinary symptoms and histological changes are associated with ultimate impaired function.

Although considerably more data is required before the exact role played by lithium in the pathogenesis of nephrotoxicity can be assessed, sufficient experience would now seem to have accumulated which will allow certain recommendations in this area to be made. Of particular interest is the association found by Hullin et al (Annex 3) between low serum lithium levels, and the low incidence of polyurea/polydypsia and raised plasma creatinine. Of equal interest is the fact that no increase in the incidence of relapse occurred until plasma levels fell below 0.4 mmol/l.
Although histological assessment was not made in this series, in view of the known functional and histological sequlae in the kidney following lithium intoxication, the maintenance of lowest effective plasma levels together with an adequate state of hydration would seem to be simple and rational measures recommend in an attempt to minimise renal damage.

Guidance with regard to the length of the treatment period, monitoring of renal, thyroid and cardiac function, and the desirability of starting long-term lithium therapy only in specific, well-defined conditions where lithium is of proven efficacy would also seem to be indicated.

Recommendations

The Committee are requested to approve guidelines for the use of lithium therapy.

[redacted]

September 1979

NOT FOR PUBLICATION

COMMITTEE ON THE REVIEW OF MEDICINES

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

GUIDELINES FOR THE USE OF LITHIUM

It is suggested that the following additions or modifications be made to the existing data sheets (see attached summary):-

Indications		Comment
	Treatment of Acute Mania Prophylaxis of recurrent bipolar affective disorders	Acute and recurrent depression omitted
Dose	Acute mania - as stated	Include to be initiated in hospital, and R.D. dosage
	Prophylaxis	
	600-1200 mg/day given in 2 divided doses to maintain plasma levels of Lithium 0.5-0.8 mmol/l	Range reduced from 0.6-1.5 mmol/l
	Children Not recommended	
	Elderly	? recommend at reduced dosage or contraindicate
Contraindications	Renal disease	
	Cardiovascular disease	
	Hypothyroidism	
	Addison's disease	
	Excessive use of diuretics	Added
	Breast feeding	Added
Pregnancy Precautions	Suggest warning as for "phasal"	

1. Lithium therapy should not be initiated unless adequate facilities for routine monitoring of blood levels are available. Add "frequency of blood sample monitors and "Blood levels to be taken" as for phasal.
2. Pre-treatment and periodic routine monitoring essential.
   Assessment of renal function, serum electrolytes, cardiac function including ECG if indicated, thyroid function and urine for sugar, before indicating treatment and regularly (?3-6 monthly).
   More frequent monitoring is required if patients are receiving diuretics.
3. Elderly patients are particularly liable to lithium toxicity.
4. Patients should be warned to report polyuria and polydypsia, episodes of nausea and vomiting or other conditions leading to salt/water depletion, including those on severe reducing diets. They should also be warned with regard to maintaining adequate salt and fluid intake.
   Clear instructions should also be given by the doctor on symptoms of impending toxicity.

Drug Interactions

Include warning re diuretics as in Camcolit.
Include statement that symptoms of nephrogenic diabetes insipidus are particularly prevalent in patients on antidpressant therapy.
Include warnings re interaction with indomethacin and tetracycline.

Adverse Reactions

Long term treatment with lithium may result in permanent changes in the kidney and impairment of renal function. High plasma levels of lithium, including episodes of acute lithium toxicity may enhance these changes. The minimum effective dose should always be used and patients should only be maintained on lithium after 3-5 years, if benefits persist. Renal function should be carefully monitored in patients with polyuria and polydypsia.
"Persistent and transient side effects", and "level of side effects and intoxication" as stated in phasal/Camcolit.
Add possible arising of psoriasis.

PRODUCTS ON THE UK MARKET CONTAINING LITHIUM CARBONATE

WITH INDICATIONS

	0108/0035 Phasal tabs 300 mg sustained release	0357/5000 Priadel tabs 400 mg sustained release	0332/0015, 5000 Camcolit 400, 250 tablets 400 mg, 200 mg.
Indications	1. treatment at acute manic or hypomanic episodes 2. prophylaxis against relapse in manic depressive disorders recurrent mania, or recurrent depression.	1. treatment of manic, hypomanic and depressive episodes 2. prophylaxis against relapse in recurrent mania, manic depressive illness and recurrent depression.	1. treatment and 2. prophylaxis of mania, manic depressive illne and recurrent depression.
2. Dose Acute mania	initially 600 mg bd increase by 300-600 mg /day if no response. Reduce dose once attack has subsided.	higher than normal doses necessary.	to be initiated in hospital 1500-2000 for 5 to 7 days, an adjusted after samples taken on 5t 7th day.
prophylaxis	600-1200 mg tabs/day in 1 or 2 doses, initially 600 mg in one dose.	1200-1600 mg as a single dose in morning or on retiring.	1000-1200 mg for 7 days, take a blood sample and adjust dose.
Children dose	not recommended		
3. Therapeutic blood levels	0.6 - 1.5 mEq/L do not exceed 2mEq/L	0.6 - 1.5 mEq/L	0.6 - 1.2 mEq/L
4. Contraindication			
renal disease	significant renal disease.	severe renal disease.	in severe renal disease.
cardiovascular disease	significant cardoivascular disease.	severe cardiovascular disease.	
hypothyroidism	hypothyroidism	frank hypothyroidism	
Addison's disease		Addison's disease	
sodium balance disorders	sodium depletion, or conditions requiring low sodium intake.		
5. Precautions			
pregnancy	not to be used in pregnancy unless alternative therapies have proved unsuccessful, and the physician considers that the benefits outweight the risks	treatment to be discontinued as a general rule during planned or continued pregancy - Li is secreted in breast milk. Babies may show signs of Li.	contra-indicated in 1st trimester. Important to ensure adequate fluid mineral intake hypothyroidism

	PHASAL	PROPHYL	BENEFIT
	Blood levels to be monitored.	toxicity, and need fluid therapy as needed.	Li. Bottle feeding should be considered
6. elderly patients	Use more cautiously as renal lithium clearance may be reduced.	recommended that starting dose is 800 mg (also if patient under 50 kg).	
7. Drug interactions			
diuretics	not to be used.	concurrent use contra-indicated.	lower doses of diuretics may be needed as diuretics reduce Li clearance Frequent monitoring of patients essenti
antidepressants	Li does not cause addiction or tolerance it maybe considered with the usual anti manic or antidepressive treatments.	all currently known antidepressant and anti manic drugs (including ECT) are compatible c priadel.	
diet	maintain a normal diet with adquate salt and fluid intake.	caution should be exercised to ensure that diet and fluid intake are normal, thus upholding a normal electrolyte balance.	

(g) Side effects and warnings	0100/0035 Phasal tabs 300 mg S-R	0357/5000 Prindel tabs 400 mg S-R	0332/0015, 5900 Camcolit 400, 250 tabs 400 mg 250 mg
(h) pre-treatment examination	pre-treatment laboratory and physical examination is required, and should be repeated periodically	estimate serium Li levels to check whether patients are receiving Li in any other form. A creatinine clearance test should be performed if necessary	clinician to assess cardiac and renal function, including ECG if necessary. Lithium renal clearance test necessary
(i) frequency of blood sample monitoring	measure blood levels weekly until stablized, and then weekly for the month after stabization, and then month monthly.	1st sample 4/5 days after starting treatment and weekly thereafter until stabilzation acheived, estimations thereafter should not exceed 3 months.	determine weekly for 1st 3 weeks in acute mania. Li levels should be monitored at least 10 - weekly when stablizied.
(j) blood levels to be taken:-	(a) on changing Li preparations (b) on appearance of prodromel toxic signs, dosage alteration development of significant intercurrent disease, signs of manic or depressive relapse, change in Na or fluid intake, or during pregnancy and parturition.	when changing from other Li preparations. Daily dose to be as close as possible to other form of lithium. During pregnancy at signs of side-effects.	
maximum blood levels occur -	within 2-4 hours of dosing.		
(k) blood samples to be taken -		before daily dose.	12 hours after last dose.
thyroid function		thyroid function tests approximately once yearly. Hypothyroidism can be treated with concurrent thyroxine.	thyroid function should be screened 3 monthly on prophylactic doses, as symptoms of depression are similar to those of early hypothyroidism. Li can impair thyroid function concurrent thyroxine can be used.

	PHASAL	PRIADEL	CAMCOLIT
just or duce doses cases o.--	early signs of toxicity.		sodium loss, impaired renal function as in exposure to extreme heat, vomiting, inter current infection, urinarytract infectio or disease.
top treatment in case f:-	intoxication, such as appearance or aggravation of drowsiness, lethargy, coarse tremor, anoresia, vomiting and diarrhoea. (See also effects).	intercurrent renal infection; only to be re-instituted when kidney function is normal again also at signs of intoxication.	
ransient side effect	infrequent below 1.5 mEq/L, mild g-i effects, nausea, vertigo, muscle weakness and a daze feeling.	unlikely below 2mEq/L fine hand tremor, mild polydipsia, mild polyuria, initial anorexia, some losening of stools more rarely mausea and diarrhoea.	mausea, loose stools, fine tremor, polyuria and polypipsia.
ersisent side-effects	fine hand tremor, polyuria mild thirst, oedema and non-toxic goitre have occurred after prolonged treatment.	weight gain and oedema may present in some patients.	find hand tremor, polyuria, and polydipsia weight gain and oedema may occur.
evel of side effect nd intoxication	aggravation of g-i effects, muscular weakness, lack of co-ordination, drowsiness, lethargy, increasing toxicity atoxia, giddiness, tinnitus blurred vision, coarse tremor, muscle hyper-irribility and polyuria. At 2-3 mEq/L increasing disorientation, coma and death.	increasing anorexia, vomiting and diarrhoea. Also mild drowsiness and sluggishness increasing to giddiness with atoxia, coarse tremor, tinnitus, blurred vision, muscular twitching, dysarthria progressing at 2-3 mEq/L to seizures coma and death.	vomiting, diarrheoa, coarse hand tremor, sluggishness, sleepiness, vertigo and dysarthria.

1. Background

1.1 Historical

Caelius Aurelionus first used mineral water with a probable high lithium content to treat mania in the 5th century AD. The element was discovered in 1817 by Arfvedson in Berzelius and various lithium salts were used during the 19th century in the treatment of gout and urinary calculi. In the early 1900s lithium bromide was used as an hypnotic and anti-epileptic, and later in the 1940s, lithium chloride was extensively used as a salt substitute. In 1949 there appeared the first report by Cade (Med. J. Aust. 2, 349, 1949) of the successful treatment of mania with lithium salts, but also in the same year, the first fatal case of lithium toxicity was reported where lithium had been used in place of salt. The toxicity associated with this use, together with the introduction of chlorpromazine in 1952 delayed the systematic use of lithium in psychiatry until the last decade. It was not until 1970 that the FDA licensed lithium for use in acute mania and in 1974 that use was extended to the prophylaxis of mania.

1.2 UK Products

There are four products with psychotropic indications currently marketed in the UK.

Priadel was first licensed in September 1968, followed by Phasal (Pharmax) in November 1973, Camcolit 250 mg (Norgine) in January 1976 and Camcolit 400 mg (originally but mistakenly thought to be a slow release preparation) in April 1977. Apart from bioavailability studies no original data on efficacy or safety has been submitted by companies. The data sheets for these preparations, together with a comparative summary of their contents, is appended.
Although licence indications are currently restricted to the treatment of mania and prophylaxis of bipolar affective disorders, a recent review of the literature (e.g, Lithium in Medical Practice, Ed. Johnson & Johnson, MTP 1978) shows at least 30 medical and psychiatric disorders where treatment involves the use of lithium.

2. Pharmacology

2.1 General

Lithium has the physical and chemical properties of other elements which belong to the first group of the periodic table, such as sodium and potassium. In general, lithium is more evenly distributed through body water than sodium or potassium, and so shows both extracellular features of sodium and intracellular features of potassium.
Like these elements, lithium has a high ionization potential and water solubility and so must influence a wide variety of physiochemical characteristics. These include pH, ionic strength, osmolarity and the biological properties of macromolecules. Theoretically therefore, lithium could influence the tertiary structure of macromolecules in cell membranes, hormone receptor sites, enzyme chains and chromosomes, and so control, directly or indirectly ionic selectivity of membranes, electrochemical gradients, responses to hormones, the coupling of energy processes to transport phenomena or even genetic expression.

2.2 Pharmacokinetics

Lithium salts are completely absorbed from the gastrointestinal tract - absorption being complete in 8 hours. Peak blood levels are reached in 0.5 - 2 hours, and plateau for 12-24 hours. Steady state plasma levels of 1.0 mg/kg are achieved in 5-6 days. Plasma half life is 18-24 hours. Lithium is not protein bound and distribution volume equals that of body water. Lithium crosses membranes slowly and enters tissues at varying rates. Peak concentration occurs in the kidney at 15 hours and in brain (rat) in 24 hours. Lithium is excreted entirely by the kidney, one-third to two-thirds of a single oral dose appearing within 6-12 hours. The remainder is excreted over 10-14 days. Discontinuation of lithium salts after chronic administration results in rapid renal excretion for the first 5-6 days, followed by slow elimination over a further 10-14 days.

2.3 Renal handling of lithium salts

The kidney handles lithium like sodium in the proximal tubule, where 60-70% of the filtered load is reabsorbed against electrical and concentration gradients. Lithium reabsorption in the distal tubules - unlike that of sodium is not quantitatively important and is insensitive to most diuretics which act distally. The effects of lithium on water flow are probably mediated through alterations in the ADH-sensitive adenylcyclase.
In sodium depletion and dehydration, as might occur during diuretic therapy or in the elderly, increased lithium reabsorption occurs, so that toxic blood levels are rapidly reached, which are aggravated by the fall in total body water. This mechanism was also responsible for the toxicity seen when lithium salts were used in the place of sodium chloride.

2.4 Mechanism of Action

The exact mechanism of action is not known - indeed any of the pharmacological actions outlined above could, singly or in combination, contribute towards the therapeutic action of lithium. Recent hypotheses include changes in amine metabolism where ion substitution in critical areas could play a major role in the synthesis, storage release and/or re-uptake of noradrenaline and 5-hydroxy triptamine, changes in carbohydrate metabolism due to the insulin like action of lithium on glucose uptake and glycogen synthesis, or alterations in electrolyte and water distribution. Patients with mania responding to lithium have the largest increases in exchangeable sodium and sodium space, compared with non-responders or controls. This finding may be associated with the increase of sodium excretion found in mania in some studies. (In Jenner F A, Bioch. Soc. Spec. Publication 1, p.101, chapter 9, 1977). Lithium also increases plasma magnesium and increases Mg-ATPase in cell membranes. The relationship of those findings to each other, and to the therapeutic effects of lithium again is not known.

2.5 Long term biochemical effects of lithium therapy

These have been summarised by K Ghose (Brit. J. of Hosp. Med, December 1977, 578) in tables 1 and 2 overleaf.

Table 1. Important biochemical changes associated with long-term lithium therapy

Function	Effects of lithium therapy
Mineral metabolism	Summarized in Table 2
Monoamine metabolism	Increased 5HT synthesis Increased noradrenaline turnover
Carbohydrate metabolism	Insulin released Increased muscle glycogen
Cyclic AMP	Inhibited
Thyroid function	Decreased synthesis of thyroid hormones
Renal function	Increased aldosterone secretion initially Distal renal tubule becomes relatively insensitive to antidiuretic hormone Probable increase in antidiuretic hormone

Table 2. Effect of lithium on mineral metabolism (data from Christiansen et al, 1976)

Mineral	Effect of lithium therapy
Sodium	Reduced concentration in central nervous system
Potassium	No significant change
Magnesium	Increased concentration in muscle and serum Decreased uptake in bone
Calcium	Increased concentration in serum Decreased uptake in bone
Phosphate	Increased uptake in muscle and liver Decreased uptake in bone
Bone mineral content	Reduced
Parathormone	Slightly increased (subclinical)

2.6 Other pharmacological effects of lithium include the potentiation of ethanol-induced sleeping time (Messiha F S, Pharmacology, 1976, 14, 153), potentiation of neuromuscular blockade by muscle relaxants (Hill et al, Anaesthesia 1977, 46, 122) and the action of pentobarbitone in mice (Diamond et al, Lancet, December 10, 1977). Several recent reports have also shown lithium to produce agranulocytosis, which effect is currently under trial in patients with drug induced granulopenia (Glenn Tisman, Lancet, July 30, 1977). Some immuno-stimulating activity has also been demonstrated by Shenkman et al (Clin. Res. 1976, 27, 634) who found increases in lymphocyte transformation and macrophase phagocytosis in lithium fed mice.

2.7 Blood levels and dosage

i. Unlike many psychotropic drugs, the administered dose of lithium bears a direct relationship to blood levels, and blood levels to clinical efficacy and toxic effects.

ii. Initially the therapeutic blood level range was considered to be 0.6 - 1.6 meq/l (as in Martindale 28th Ed) but most investigators feel 1.6 meq/l is in the toxic range. Salkind (J. Royal Col. Gen. Pract, 20, 13, 1970) suggested a range of 0.6 - 1.5 meq/l, and Schou (Br. J. Psychiatr. 116, 615, 1970) and Bennie et al (Lithium in Med. Practice, 1978, p.381, ed. Johnson & Johnson, MT Press) thought the most suitable range to be 0.7 - 1.2 meq/l. When the patient is standardised, a dosage of 600 mg - 1600 mg will usually achieve these levels. As the therapeutic range is narrow, regular monitoring is essential, particularly during the initial stabilization period. Blood levels should be sampled at the same time after each dose.

iii. Toxic symptoms (see below) occur with blood levels of 1.6 - 3.0 mmol/l with death occurring with levels from 3.0 - 4.0 mmol/l.

iv. Although lithium has a long half life and theoretically could be given once per 24 hours, the highest blood level peak falls within the toxic range and BD administration is advisable. Recent studies have shown sustained release preparations are as effective as ordinary preparations, and compared with BD administration, are less likely to reach toxic levels.

3. Toxicity

3.1 Adverse Reactions

The side effects of lithium therapy fall into three general areas - those usually minor symptoms occurring when blood lithium levels are within the normal therapeutic range, those serious symptoms occurring with high blood lithium levels i.e, lithium toxicity, and adverse reactions occurring with chronic lithium administration.

i. Early side effects

Minor side effects are common, especially when first starting therapy. These include nausea, intestinal upsets, thirst, polyuria, skin rashes and tremors, and occur even though blood levels are within the therapeutic range. These effects may lessen following dose stabilization.

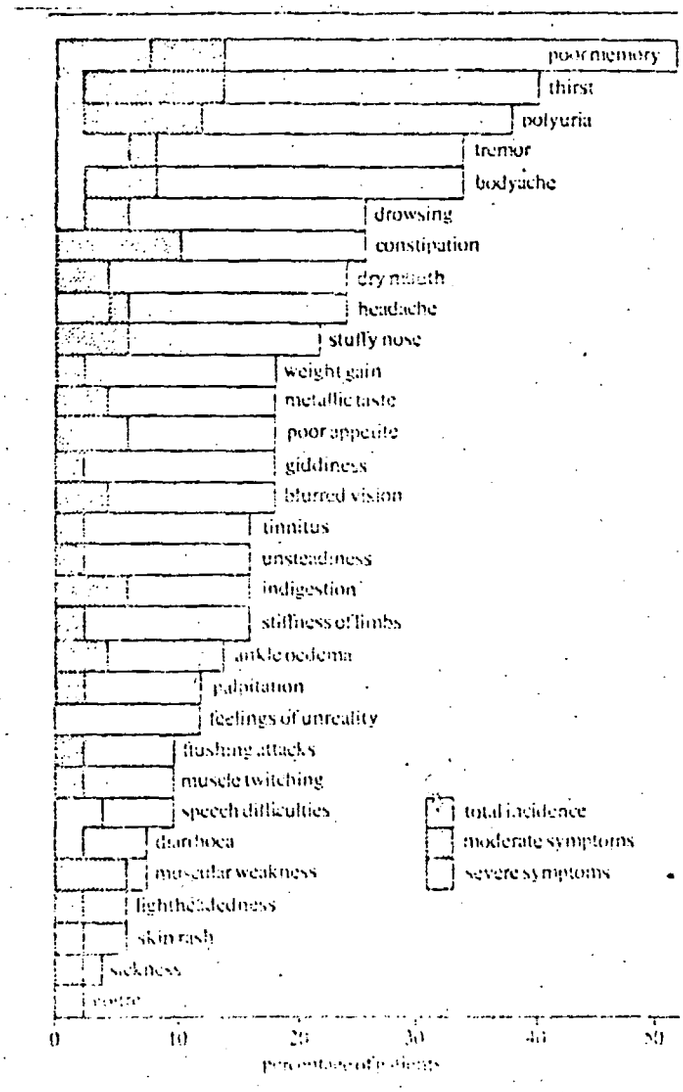
ii. Lithium toxicity

In general, the occurrence and severity of lithium toxicity is directly proportional to lithium blood levels. Normal therapeutic blood levels of 0.6 - 1.5 mmol/l can be associated with lithium toxicity in the elderly, in patients with pre-existing brain damage, in schizophrenia, and in association with some drugs given concomitantly with lithium (see below).

In most patients symptoms of toxicity occur with blood levels approaching 2.0 mmol/l. These include blurred vision, tremor, ataxia, diarrhoea and dysarthria and patients should be warned of the significance of such symptoms. Blood levels of 2-4 mmol/l lead to disorientation, cardiac arrhythmias, muscle hyperactivity, convulsions, coma and death, or irreversible brain damage. Dehydration and sodium depletion from any cause result in lithium retention and raised plasma levels leading inevitably to severe toxicity. Most diuretics (see below) are particularly dangerous in this respect, and a recent case of lithium toxicity has been reported following dieting and saunas (Tonks, BMJ, 26 November 1977, p.1396). Treatment of lithium toxicity includes sodium and fluid replacement and peritoneal dialysis.

iii. Long term treatment

Common symptoms occurring during long term treatment, include polyuria, polydypsia, fine finger tremor, weight gain and hypothyroidism. The pathological effects on the kidney, thyroid and heartare the most serious to occur and will be considered in more detail below. The incidence of subjective symptoms in patients receiving lithium therapy at the MRC Neuropsychiatry Laboratory have been reported by K Ghose in B. J. of Hosp. Med. December 1957, 578, and are reproduced below.



iv. Other

Three cases of diabetes mellitus have recently been reported following long term lithium therapy (Craig et al, Lancet, November 12, 1028, 1977; B B Johnston, Lancet, October 29, 935, 1977).
Two cases of lithium induced nephrogenic diabetes have also been reporte by Price et al (Ann. Int. Med 88, 536, April 1978) where blood lithium levels were within the therapeutic range.

The Swedish Adverse Drug Reaction Committee (Notice 26, May 1977) have described 9 cases of exacerbation of psoriasis where patients were treated with lithium. The causal relationship between lithium and psoriasis was established by the time course on introducing and withdrawing the drug. As lithium is known to inhibit adenylcyclase activity, and the content of cyclic AMP in psoriatic skin is reduced, it is thought that lithium may elicit or worsen psoriasis by interfering with this system.

3.2 Lithium and the kidney

The major target of lithium toxicity to emerge over the last decade is the kidney. Although polyuria and polydypsia have been known to occur frequently during lithium treatment, and early animal studies by Schou showed the kidney to be a target organ of toxicity in animals, the occurrence of these symptoms have not been thought indicative of serious or progressively deteriorating renal function. Recent studies over the past year or so, however, have shown that irreversible histological changes can occur in association with normal therapeutic blood levels of lithium. This finding, in the opinion of some investigators, could lead to a reconsideration of the criteria used for long term lithium use. As there is current interest and controversy regarding the relevance of lithium produced changes and the kidney, this topic is discussed in some detail.

Animal Studies

i. In 1958, Schou found high doses of lithium given to rats produced oliguria, azotemia, lithium retention and irreversible renal tubular damage. A high sodium diet gave some protection (Acta Pharmacol. Toxicol 15, 70, 1958).

ii. Evan in 1972 (Evan & Ollerich, Am. J. Anat. 134, 97, 1972) showed lithium carbonate given in therapeutic doses (10-30 mg/kg) in cats and dogs gave ultramicroscopic mitochrondrial damage in the distal hephron. The reversibility of the lesion was not determined.

Human studies

i. Acute changes during lithium toxicity

A number of authors including Schou et al (J. Psych. Res. 6, 67, 1968) have found raised blood urea, serum creatanine and oliguria in patients with lithium toxicity. These symptoms are usually reversible.

ii. Diabetes Insipidus

Chronic lithium administration is known to impair concentrating and acidifying abilities in man and animals (Bucht & Wahlin, Lancet April 8, 1978, p.778). At least one-third of lithium treated patients have ADH unresponsive diabetes insipidus. Some 55 articles on lithium induced polyuria and polydypsia have now appeared, giving the incidence of some degree of diabetes insipidus as over 40%. In most patients the symptoms seem mild and well tolerated. The possible mode of action of lithium is thought to be associated with the inhibition of ADH-sensitive renal adenylcyclase. Lithium significantly inhibits ADH induced water transport in the toad bladder but does not affect c AMP-induced water flow. A possible central action of lithium on ADH synthesis/storage/ release mechanisms might also be involved.

iii. Histological Changes.

a. Hestbech et al (Kidney Int. 1977, v.12, p.205) published one of the first studies showing histological kidney changes in human patients. In 13 out of 14 patients with acute lithium intoxication, he found focal nephron atrophy and/or interstitial fibrosis. Sclerotic glomeruli were five times as common in patients on lithium compare with age matched controls, tubular atrophy three times as common and lithium patients had twice as much connective tissue. These patient showed proteinuria only during the period of acute intoxication - otherwise no significant findings referable to the kidney function were seen.
In a second study by the same authors involving 13 (8 from the above series) with structural kidney changes, only osmolar concentrating deficiencies were seen.

b. Burrows, Davies & P. Kincaid-Smith (Lancet, 17 June 1978, p.1310) in a letter to the editor, reported histological kidney lesions in 5 patients who had received lithium therapy for 4 months to 9 years. They described a "unique tubular lesion" in the distal convoluted and collecting tubules, which included PAS positive granular material in the wall of cells radiating from the nuclei and large intense staining in the cytoplasm of cells before other damage was visible. Amorphous PAS positive casts were also prominent, as well as ballooning and vacuolation of cells and cytoplasm. Only minor changes were observed in the proximal tubules Changes were more advanced the longer the patient had received lithium - some 20% of glomeruli were seen to be sclerosed with tubular atrophy and interstitial fibrosis.
Renal function in these patients was normal and urine contained neither protein or excess RBCs i.e, the usual indications for renal biopsy were absent. Because of the apparent progressive nature of the lesion, in spite of normal function, these authors considered that long term lithium treatment should be reserved for the treatment of bipolar affective disorders only and, that tricyclics should be used in patients with recurring depression, in the absence of cardiac problems.

c. Inpharma (13 May 1978, p.6) note that 3 further cases of impaired kidney function and biopsy confirmed renal pathology had been report at the Scandinavian Soc. of Psychopharmacology. The figures reporte suggested a 15-20% incidence of renal pathology in lithium treated patients. However they also considered terminal azoteamia unlikely to develop and that most risk from the kidney was likely to be due to a decreased urine concentrating ability leading to dehydration, and an increased risk of lithium toxicity.

d. Schou & Jenner (Lithium in Medical Practice, MTP 1978) have both suggested that life long lithium therapy must be weighed against not only the histological lesions but functional abnormalities of the kidney and the quality of life which may be lithium dependent Both investigators feel that renal insufficiency is uncommon in long term lithium patients and that if only the capacity to concentrate urine appears to be impaired, life need not be endangered.

3.3 Lithium and cardiovascular effects

Adverse effects of the heart, including reversible flattening or inversion of T waves and arrhythmias have been reported (Jaffe, Am. J. Psych. 1977, 134, 88; Demess et al, Dis. of Nerv. Syst. 1970, 31) and the safety of long term lithium therapy in patients with cardiovascular disorders has been questioned. In a recent review of the cardiovascular effects of lithium in man, however, Tilkian et al (Am. J. of Med. 1976, 61 (5), 665) has shown significant CVS effects such as hypotension and "cardiovascular collapse" occur only in severe lithium toxicity. On normal therapeutic doses T wave flattening and, rarely, sinus node dysfunction and ventricular arrhythmias can occur, but are reversible. He concludes that lithium is safe to use if dose is adjusted to rate of lithium excretion with close monitoring of serum levels.
In patients with cardiac arrhythmias Tilkian advises frequent ECG monitoring and points out that patients with congestive cardiac failure or on salt restriction are particularly liable to lithium toxicity.
In experimental animals, lithium produces hypercalcaemia and hypermagnesaemia with associated ECG changes.

3.4 Lithium and the thyroid

Schou first reported in 1968 (BMJ, 1968, 3, 710) the occurrence of hypothyroidism in patients taking lithium carbonate or sulphate. The incidence of thyroid deficiency is now considered to be 5-15% (Lindstedt et al, Br. J. Psych. 1977, 130, 452: Lazarus and Bennie, Acta Endocrinologia 1972, 70, 260).
Two cases of irreversible myxoedema, without goitre, have recently been reported (Persild et al, BMJ, 1108, 29 Apr. 1978)
Goitre can also occur, with or without symptoms of hypothyroidism.
Lithium appears to inhibit the release of iodine T_3 and T_4, from the thyroid gland so that decreased circulatory levels peripherally, stimulate TSH production resulting in thyroid enlargement.

Berens & Wolff (Lithium Research and Therapy, ed. Johnson, Ac. Press, 1975, p.445) reported that out of 330 patients developing goitre over 5-24 months of lithium therapy, none were clinically hypothyroid and the overall incidence of goitre was 4%. In other series however, up to 20% of patients with goitre have been clinically hypothyroid. Lithium may also produce abnormal laboratory tests in the presence of clinical euthyroidism. Christiansen et al (Neuropsychobiology, 1975, 1-344) has reported that hypothyroidism is more likely in woman and may be accompanied by raised serum calcium and magnesium concentrations. Perez et al (Clin Pharm. & Therap. 1977, 21, 449) has suggested that these changes may be due to direct action of lithium on the parathyroid glands. Lithium induced thyrotoxicosis has also been reported (Franklin, New Zealand M. J. 1974, 79, 782).

3.5 Drug Interactions

i. Introduction

In general the use of lithium with other drugs is fairly well tolerated. The most serious consequences are seen with diuretics and possibly with some neuroleptics, such as haloperidol. These are discussed in some detail below. Lithium apparently does not adversely interact with the tricyclic antidepressants, and may even act synergistically (Lingjaerde et al, Acta Psychiatr. Scand. 50, 233, 1974).
No adverse reactions have been reported with either the MAOIs or orally administered anxiolytics, although a recent report has appeared of hypothermia occurring when iv diazepam was used in a patient on lithium therapy (Murphy, BMJ, 2 July 1977, 642).

ii. Lithium and diuretics

The excretion of lithium is closely linked with that of sodium in the kidney and most clinically used diuretics on a long term basis can be expected to cause lithium retention, high serum levels with a corresponding higher risk of lithium toxicity. The mechanism is thought to be due to both reduced renal clearance of lithium with thiazides - which Penst et al found to be 26% in normal volunteers (Psychopharmacol. Commun. 2, 273, 1976) and reduction in total body water and sodium by action of the diuretic. Salt restriction and dehydration exacerbate the high risk of severe toxicity.

iii. Lithium and haloperidol

Toxic neurological symptoms including rigidity, ataxia, and tardive oral dyskinesia, have been reported by Cohen & Cohen (JAMA, 230, 1283, 1974); Mashold et al (Act. Nerv. S[illegible] 16, 199, 1974) and London and Wering (Lancet ii 1088, 1976), when lithium is used in combination with haloperidol. These authors suggest that neurotoxicity including irreversible brain damage can occur when haloperidol is used in doses of over 40 mg/day when blood lithium levels are maintained at 1 mmol/l or over. However, Baastrup et al (JAMA 236, 2645, 1976) reviewed 425 hospital patients treated simultaneously with both lithium and haloperidol and found the incidence of adverse reactions the same as in patients treated with either drug alone. These authors, on reviewing Cohen & Cohen's cases found, because of the mixed drug history, a direct relationship between a combined lithium and haloperidol therapy and neuro-toxicity difficult to establish.

iv. Miscellaneous drug interactions

a. Chlorpromazine. A study by Kerzner et al (Clin. Pharmacol. Ther. 19, 109, 1976) suggests that concurrent administration of chlorpromazine with lithium may depress lithium blood levels due to delayed stomach emptying.

b. Methyldopa. Methyl-dopa may increase lithium toxicity even though blood levels are within the therapeutic range. Two cases have so far been reported.

c. Anticonvulsants. Speirs & Hirsch (in Lithium in Medical Practice, MTP 1978) report lithium toxicity with normal blood levels in a patient concomitantly receiving phenytoin and phenobarbitone. Serum lithium decreased following initial stabilization, and doubling the dose to 2000mg/day produced blood levels of 0.8 mmol/l. Toxic symptoms included diarrhoea, tremor and coma. The patient recovered after complete lithium withdrawal.

d. Neuromuscular Blocking Agents. Two reports are also available which suggest that lithium may prolong the action of the nondepolarising neuromuscular blocking agents - pancuronium bromide and succinyl chloline. This action of lithium has been confirmed in animals (Reimherr et al, Am. J. Psychiat. 134, 205, 1977).

4. Teratology

4.1 Animals

High doses of lithium in animals show in general an increased tendency towards impaired fertility and malformations in the offspring, particularly with parenteral preparations and high single daily doses. Graffa & McIlpenny however, found no abnormalities in rats when lithium was given in divided doses at therapeutic levels (Pharmacol. 21, 428, 1972).

4.2 Humans

Since 1968 a Scandinavia register has been kept for babies born to mothers receiving lithium. A similar register is kept in California.

In 1977, 166 babies had been born to mothers who had received lithium carbonate during the first trimester of pregnancy. Of these 18 had malformations, the greatest number involving the heart and major blood vessels. Nora et al (Lancet 2, 594, 1974) reporting on 13 lithium babies showed 10 to have abnormalities involving the heart and great vessels (4 having Ebsterin's malformation of the tricuspid valve) and 1 an abnormality involving the umbilical artery.

A follow-up at 5 yrs of 60 of the normal babies born to lithium mothers on the Scandinavian register showed no significant difference with regard to developmental abnormalities between these and controls.

4.3 Chromosome Studies

Friedrich & Nielsen found chromosomal abnormalities in in-vitro studies with human leukocyte chromosomes at concentrations of 2-4 mg/l - (Lancet 2, 435, 1969).
Ten chromosome breaks in seven out of eight infant leukocytes were also seen in a baby with multiple deformities born to a mother with acute lithium toxicity during pregnancy (CMA, Oct 23, 1971, 105). However, Weinstein & Poldfield (Am. J. Psych. 132, 529, 1975) found that lithium at therapeutic concentrations had no significant effect on chromosomes in man.

4.4 Lithium intoxication in the newborn

Hypotonic, floppy listless babies have been reported to have been born to lithium toxic and non-toxic mothers. The babies usually recover without special treatment (Woody et al, Paediatrics 47, 94, 1971). Two cases of tyroid abnormality have been reported in the newborn.

4.5 Breast Feeding

Lithium passes into breast milk at half the plasma concentration.

5. Therapeutic Efficacy

5.1 Treatment of acute mania

Following Cades original observation in 1949, lithium after a slow start, has now become the treatment of choice for mania and hypomania. In 1968

Schou reviewed 32 publications (J. Psychiat. Res. 6, 67, 1968) of which 31 demonstrated the therapeutic efficacy of lithium in acute mania. Numerous more recent studies have confirmed that lithium can be expected to control the symptoms in acute manic patients in 70-80% of cases (ref. in Lithium Research & Therapy p.25, ed. F N Johnston, Ac. Press 1975).
Relapse following withdrawal of treatment was demonstrated by Burney et al (Am. J. Psychiat. 125, 499, 1968) and the therapeutic superiority of lithium to chlorpromazine in the highly disturbed acutely manic has been shown by Warton & Fiene (Am. J. Psych. 123, 706, 1966) and Takahashi et al (Arch. G. Psych. 32, 1310, 1975).

In gneral, the effect of lithium is seen 5-10 days after starting therapy, but maximum effectiveness may not be seen for some weeks or even months. It appears to benefit mostly patients with the pure elation, hyperactivity, pressure of speech syndrome rather than patients with delusions and hallucinations.

5.2 Prophylaxis of mania and bipolar affective disorders

i. Recurrent Mania

Early studies which suggested that lithiumwas effective in preventing as well as treating recurrent attacks of acute mania, were criticized in 1968 by Blackwell & Shepherd (Lancet, May 4 1968, 968) as being mainly open trials which failed to establish efficacy in the prophylaxis of mania. In 1970, Baaskrup et al (Lancet, ii, 326) carried out a double blind, randomised trial where placebo or lithium was given to patients already receiving lithium. The relapse rate was strikingly different between the two groups. Subsequent experience has confirmed the efficacy of lithium in the prophylaxis of recurrent mania and hypomanic states (Lithium in Medical Practice, MTP, 1978).

ii. Bipolar affective disorders

a. The efficacy of lithium in prophylaxis of the recurrent depressive pole of the illness has taken longer to establish. However, the conclusion in 1975 of the American Psychiatric Association task force on lithium therapy (reported in Primer of Lithium Therapy, J W Jefferson and J M Preis, Williams & Wilkins 1977, p.18) was that "lithium is effective in the prophylaxis of bipolar affective illness with regard to both the manic and depressive symptoms". Efficacy of lithium in an illness which is mainly depressive is less well established, although the above task force also concluded that there was "persuasive evidence from controlled studies that (lithium) is also effective in the prophylaxis of unipolar depressive illness". They warned of the necessity of exactness in definition of unipolar illness and the need for further trials.

b. Anath et al (J. Clin. Psychiatry 39, 95, 1978) have recently reviewed the use of lithium in recurrent depression, and has emphasized the relationship of precise diagnosis to a high incidence of "good responders". These authors suggested that a good therapeutic effect could be predicted in 80-90% of patients with depressive symptoms if (1) a definite diagnosis of primary affective disorder had been made,
(2) less than 4 episodes of mania and depression occurred per year,
(3) psychotic features were present during manic and depressive episodes (e.g. grandiose, elated, during mania etc) and that
(4) there was a family history of bipolar illness with response to lithium by affected members.

The search of identification of "good responders" has shown some biochemical differences between those responding to lithium therapy.
Flennenbaum et al (Am. J. Psychiat. 336, Mar. 1978) found a higher red blood cell/plasma lithium ration (0.41) in a study of 33 depressive unipolar 'responders' after 17 months of lithium therapy which als included schizo-affective psychoses and alcoholics. Sullivan et al (Lancet, Dec. 1977, 1325) showed that platelet MAO activity of resonders in manic depressive psychosis similar to that of normal controls whereas that of non-responders was less.

Although some authors feel that the role of lithium with regard to recurrent depressive symptoms is not fully defined and that patients with bipolar illness are more likely to respond than those with recurrent unipolar depression (e.g, Threndels 1976, reviewed 9 uncontrolled and 10 uncontrolled trials showed statistically significant results in only 3 of the ten controlled trials), Schou has recently stated (Lithium in Medical Practice, p.21 ed. F N & S Johnson, MTP, 1978) that "efficacy (of lithium) in prophylaxis in recurrent affective disorders is now well established. Lithium will either attenuate or prevent depression in monopolar as well as bipolar disorders". Lithium is not approved by the FDA however, for either the prophylaxis or treatment of unipolar depression.

5.3 Treatment of Acute Depression

E H Bennie has recently summarised the results of 14 clinical studies where lithium has been used in the treatment of acute depression (Lithium in Medical Practice, MTP 1978). The results are summarised below:-

Type of Study	Uncontrolled Studies	Controlled Studies
Number of patients	189	128
Number responding to Lithium	110	51 (77)*
% improvement	52	40 (60)*
Number of studies	9	5

* Partial response.

It is evident from these results that tricyclic antidepressants or ECT are considerably more effective in the treatment of acute depressive illness. The task force of the American Psychiatric Assocn (1975) concluded that "experimental results are not sufficiently conclusive to permit a clear definition of the value of lithium in acute depression".

6. Medical Comment

Over the past 10-15 years, lithium has become established as the treatment of choice in acute mania and in the prophylaxis of recurrent bipolar affective disorders. Although the exact mechanism of action is unknown, it appears to have a specific, rather than general, effect in patients with recurrent mania. This point is illustrated by relatives observing that the patients "appear their normal selves and not drugged" when responding to lithium therapy (Jenner in Lithium in General Practice, MTP 1978).

In recurrent affective disorders where depressive symptoms predominate, efficacy of lithium is less well established. Successful treatment in these patients may depend upon the recognition by meticulous history taking, strict diagnostic criteria, and possibly biochemical means of a specific subgroup of "lithium responders". Lithium appears to be of little benefit in the treatment of acute depressive illness.

In general, lithium is well tolerated and, with the exception of diuretics and possibly some neuroleptics, can be administered concurrently with other drugs with relatively few untoward effects.
The major acute problem is lithium toxicity - which occurs when blood levels exceed 1.6 mmol/l and is precipitated and accelerated by dehydration, salt restriction and diuretics.
Adequate instructions to patients regarding the circumstances and symptoms of impending toxicity have been found to minimise this problem. Particular care in monitoring should also be taken of patients with cardiovascular disease.

The major side effect of chronic lithium treatment - and the one which is of current concern, is the problem of irreversible kidney damage. Although histological changes have been found in the kidney following months to years of therapy (and in the absence of lithium toxicity) the relationship of these changes to function - other than impairment of concentration and acidifying ability is not known. In the absence, so far, of reports on chronic renal failure occurring, most investigators feel that as long as strict diagnostic criteria are observed in prescribing long term lithium therapy the risks are justified by the improvement in the quality of life experienced by patients responding to lithium (see recent reports on Lithium and Kidney, appended, Annex 3).
Early detection by regular monitoring of both renal (including urine for sugar) and thyroid function might prevent the development of severe progressive lesions occurring in the tissues.
Theoretically, lithium with its long half life, could be administered in a single daily dose. Reports have shown, however, that even with sustained release preparations, blood levels peak in the toxic range so that BD administration would seem desirable. There would seem to be relatively little difference between the available preparations, particularly as therapeutic blood levels are maintained by biochemical control.

Although 95-98% of babies born to mothers receiving lithium are normal, lithium has been shown to cause teratogenic abnormalities, particularly of the heart and great vessel, so that this risk must be weighed against any therapeutic benefit.

7. Recommendations

The Committee might consider the following modifications or additions to be made to the data sheets of lithium products:-

1. Indications — Treatment of acute mania - Prophylaxsis of recurrent bipolar affective disorders (Acute and recurrent depression omitted).

2. Dose levels — As stated - but twice daily.
Children. Not recommended.

3. Therapeutic Blood Levels — 0.6 - 1.2 meq/l/mmol/l

4. Contraindications — As for Phasal - plus Addison's disease.
Add - excessive use of diuretics; breast feeding.

(P) 5. Pregnancy — As stated.

(P) 6. Elderly patients — Include warning.

(W.A.E.) 7. Drug Interactions

Diuretics - as stated.
Antidepressants - as stated.
Diet - as for Priadel.

Add warning regarding possible interaction with Haloperidol and any drugs which may lead to dehydration or salt depletion

8. Side effects and warnings

(P) (i) Pre-treatment and periodic routine monitoring. — assessment of renal function, serum electrolytes; cardiac function with ECG if indicated. Thyroid function. Urine for sugar. Add close monitoring is essential if diuretics necessary or in patients with cardiac disease.

(W) (ii) Frequency of blood monitoring and (iii) blood levels to be taken — As for phasal. Add exposure to extreme heat, intercurrent infection, urinary tract infection or disease, as in Camcolit.

(W) (iv) Time — Take blood sample (same time after each dose).

(W) (v) Stop treatment in case of — as for phasal and priadel. Add clear instruction to doctor to inform patients of symptoms of impending toxicity. Add Warning regarding delay in therapeutic action.

(SE) SIDE EFFECTS

(SE) Transient side effects - infrequent below 1.5 meq/l, other as stated

(SE) Persistent side effects - as stated.

Level of side effects and intoxication - as stated - see warning 8 (vi) above.

Add (a) warning re worsening of psoriasis.

(b) possible long term effects on kidney.

(c) diabetes.

PHASAL

Pharmax Ltd

PHASAL*

Presentation White tablets of diameter 0.5 inch, marked on one side with 'P' inside a hexagon. Each Phasal contains 300 mg Lithium Carbonate BP in a sustained release presentation.

Uses Lithium is an antimanic agent; it can also exert a stabilising influence on recurrent affective disorders. Recommended uses:

1. Treatment of acute manic or hypomanic episodes.
2. Prophylaxis in manic-depressive disorders, recurrent mania or recurrent depression.

Dosage and administration Dosage must be adjusted in the individual patient according to clinical condition and the results of regular blood lithium determinations.

1. Acute episode: Initially 2 tablets b.d. Increase by 1 or 2 tablets per day if no response. Maintain blood lithium levels in optimum range 0.6–1.5 mEq/l; do not exceed 2 mEq/l. Dosage should be reduced rapidly once the acute attack subsides.

2. Prophylaxis: Usually 2–4 tablets per day administered in 1 or 2 doses. Maintain blood lithium levels in range 0.6–1.5 mEq/l.

When starting directly on prophylactic therapy administer 2 tablets in a single dose initially, with subsequent increments of 1 tablet until adequate blood levels are achieved. When changing from an alternative lithium preparation administer the same daily dosage initially and modify if necessary according to blood-level determinations.

Blood-level monitoring: Blood levels should be determined by taking a blood sample before the daily dose. Initially this should be done four to five days after commencing Phasal treatment. Weekly checks are recommended for the month following stabilisation, and then monthly determinations may suffice. With lithium preparations maximum blood levels normally occur within two to four hours of dosing. Blood levels should also be determined on the following occasions: appearance of prodromal toxic signs, dosage alteration, development of significant intercurrent disease signs of manic or depressive relapse, significant change in sodium or fluid intake, or during pregnancy and parturition.

Phasal does not cause addiction or tolerance. It can be safely combined with the usual antimanic or antidepressive treatments.

Tablets must be swallowed whole.

Contra-indications, warnings, etc

Contra-indications: Significant renal or cardiovascular disease, hypothyroidism, sodium depletion, or conditions requiring low sodium intake.

Precautions: Pre-treatment laboratory and physical examination is required, and should be repeated periodically.

The patient should be advised to maintain a normal diet with adequate salt and fluid intake. Diuretics should not be used during lithium therapy.

Lithium intoxication seldom occurs suddenly. The patient must be instructed to discontinue therapy and report to the doctor should prodromal toxic signs occur, such as appearance or aggravation of drowsiness, lethargy, coarse tremor, anorexia, vomiting or diarrhoea (see also 'Adverse effects').

Phasal should not be used in pregnancy or women of child-bearing potential unless alternative therapies have proved unsuccessful and the physician considers the potential benefits outweigh the possible hazards.

Phasal should be used more cautiously in the elderly, in whom renal lithium clearance may be reduced.

Phasal is not recommended for use in children.

Adverse effects: Side-effects are usually related to blood lithium levels, and are infrequent at levels below 1.5 mEq/l. Mild gastro-intestinal effects, nausea, vertigo, muscle weakness and a dazed feeling may occur, but frequently disappear after stabilisation. Fine hand tremor, polyuria and mild thirst may persist. Oedema and non-toxic goitre have occurred in some patients following prolonged treatment.

Appearance or aggravation of gastro-intestinal effects, muscular weakness, lack of co-ordination, drowsiness or lethargy may be early signs of intoxication. With increasing toxicity there is ataxia, giddiness, tinnitus, blurred vision, coarse tremor, muscle hyperirritability and a large output of dilute urine. At blood levels above 2–3 mEq/l, there is increasing disorientation, seizures, coma and death.

Overdosage: Early signs of toxicity usually respond to reduction or cessation of dosage.

There is no specific antidote for lithium poisoning. Treatment comprises general supportive measures and maintenance of electrolyte balance. Elimination of lithium may be facilitated by infusion of sodium bicarbonate, acetazolamide, urea or mannitol.

Prolonged continuous peritoneal dialysis may be more effective than haemodialysis.

Pharmaceutical precautions Store in a cool dry place.

Legal category POM.

Package quantities Securitainers of 100 and 500 tablets.

Further information Phasal is a sustained release preparation designed to facilitate control of blood lithium levels within the optimum range. The smaller diurnal variation produced by the once or twice daily dosage regimen: (i) reduces the risk of rapid and excessive absorption of lithium and thereby improves safety; (ii) maintains the desired blood levels and so provides continuous protection against relapse; (iii) improves convenience of dosing for the patient.

Product licence number 0108/0035.

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PRIADEL®

Presentation Controlled release lithium carbonate tablets; white circular, scored bi-convex tablets engraved PRIADEL one side. Each tablet contains 400 mg Lithium Carbonate BP in a controlled release dosage form.

Uses Controlled release lithium therapy for:

a) The treatment of manic, hypomanic and depressive episodes of recurrent affective disorders.

b) Prophylaxis against relapse in recurrent mania, manic depressive illness and depressions

Dosage and administration A simple treatment schedule has been evolved, which, except for some minor variations, should be followed whether using PRIADEL therapeutically or prophylactically. The minor variations to this schedule depend on the elements of the illness being treated and these are described later.

1. In patients of average weight (70 kg), 3–4 tablets (1,200–1,600 mg) of PRIADEL are given as a single daily dose in the morning or on retiring. In elderly patients or those below 50 kg, it is recommended that the starting dose be reduced to 2 tablets (800 mg). The tablets should not be crushed, chewed or swallowed with hot liquids. When changing from other lithium preparations, serum lithium levels should be first checked, then PRIADEL therapy commenced at a daily dosage as close as possible to the dosage of the other form of lithium.

2. Four to five days after starting treatment (and never longer than one week), a blood sample should be taken before the daily dose of tablets for the estimation of serum lithium levels.

3. If necessary, the dose of PRIADEL is adjusted by half to 1 tablet to maintain serum lithium levels between 0·6–1·5 m.mol/L (=mEq/L). Serum lithium levels should be monitored on a weekly basis until stabilisation is achieved.

4. Following stabilisation of serum lithium levels, the time interval between subsequent estimations can be gradually increased, but should not normally exceed three months

5. Careful clinical appraisal of the patients should be exercised throughout medication.

6. Priadel should be continued through any recurrence of the affective disturbance. This is important as the full prophylactic effect may not occur for 6–12 months after the initiation of therapy.

7. Thyroid function tests should be performed approximately once yearly. A small number of patients may show drug induced hypothyroidism which may be treated successfully with concurrent thyroxine.

Treatment of acute mania and hypomania: It is likely that a higher than normal PRIADEL intake may be necessary in the acute phase. Therefore, as soon as control of the mania is achieved, the serum lithium level should be determined and it may be necessary, dependent on the results, to lower the dosage of PRIADEL and re-stabilise serum lithium level. In all other details, the described treatment schedule is recommended.

Prophylaxis against recurrent mania and hypomania, manic depressive illness recurrent depression and treatment of depression: It is recommended that the described treatment schedule is followed.

Contra-indications, warnings, etc When contemplating Priadel therapy ascertain whether patients are receiving lithium in any other form; if so check serum levels before proceeding. It is important to ensure that renal function is normal; if necessary a creatinine clearance test or other renal function tests should be performed. Renal insufficiency, cardiac insufficiency, Addison's disease and frank hypothyroidism are all contra-indications to lithium therapy. Treatment should be discontinued during any intercurrent renal infection and should only be reinstituted when kidney function has returned to normal.

Caution should be exercised to ensure that diet and fluid intake are normal, thus maintaining a normal electrolyte balance. This may be of special importance in very hot weather. Infectious diseases including colds, influenza, gastro-enteritis and urinary infections may alter fluid balance and thus affect serum lithium levels.

Although there are reports of the safe use of PRIADEL during pregnancy it is recommended as a general rule that PRIADEL be discontinued during a planned or confirmed pregnancy. If it is considered essential to maintain Priadel treatment during pregnancy serum lithium levels should be closely monitored since renal function alters gradually during pregnancy and suddenly at parturition, thus requiring dosage adjustments. Babies may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Lithium is secreted in breast milk and bottle feeding is recommended.

Side-effects: Transient side-effects may occur during during the stabilisation but are unlikely to do so at serum lithium levels below 2·0 m.mol/L. They are most commonly a fine tremor of the hands, mild polydipsia, mild polyuria, initial anorexia, some loosening of the stools and, more rarely, nausea or diarrhoea. In these cases it is advisable to check serum lithium levels. Weight gain or oedema may present in some patients.

Toxic effects: Such effects are indicative of impending lithium intoxication and they fall into two groups

a) Gastro-intestinal: increasing anorexia, diarrhoea and vomiting.

b) Central nervous system: mild drowsiness and sluggishness increasing to giddiness with ataxia, coarse tremor of the extremities and lower jaw, tinnitus, blurred vision, muscular twitching, dysarthria progressing (above 2–3 m.mol/L) to seizures, coma and death.

If any of the above symptoms appear, the patients should be instructed to stop taking their tablets and report for an immediate serum lithium estimation.

Lithium intoxication: There is no specific antidote to lithium poisoning, in the event of accumulation lithium should be stopped and serum estimations should be performed every six hours to ensure that the lithium level is falling at a rate corresponding to a half life of under 30 hours.

Under no circumstances should a diuretic be used. Intravenous osmotic diuresis (Mannitol or urea infusion) or alkalinisation of the urine (sodium lactate or sodium bicarbonate infusion). If there is a deterioration in the patient's condition, or if the serum level is over 4 m.mol/L, peritoneal or haemodialysis should be promptly instituted. This should be continued until there is no lithium in the serum or dialysis fluid. Serum lithium levels must be monitored for at least a further week to take account of any possible rebound in serum lithium levels as a result of diffusion from body tissues.

Drug interactions: Any drugs affecting electrolyte balance (e.g. diuretics, appetite suppressants, steroids) may alter lithium excretion and should be avoided in patients on lithium. If other psychotropic drugs are used they should be initiated at a lower dosage than usual as their side-effects may be potentiated by the use of lithium. This has been shown to be of particular importance for the concurrent use of lithium and haloperidol.

Pharmaceutical precautions Cool conditions of storage required. Tablets should not be crushed, nor any attempt made to dissolve them before administration.

Legal category POM

Package quantities Tubes of 100 and 1,000 tablets. Fibre drums of 10,000 tablets.

Further information Nil.

Product licence number 0357/5000.

CAMCOLIT®

Presentation *Camcolit 250:* White uncoated tablets, engraved on one side 'Camcolit' each containing 250 mg Lithium Carbonate BP (equivalent to 6.8 millimoles).

Camcolit 400: White uncoated tablets, engraved one side 'Camcolit S' with break line on reverse side, each containing 400 mg Lithium Carbonate BP (equivalent to 10.8 millimoles).

Uses Treatment and prophylaxis of mania, manic-depressive illness and recurrent depression.

Dosage and administration Tablets for oral administration.

Treatment of mania and hypomania: The requisite daily dosage may be administered at the discretion of the clinician, either in divided doses or as a single daily dose. Some clinicians prefer to prescribe Camcolit 250 for divided doses and Camcolit 400 for a single daily dose regime.

Treament of mania should be initiated in hospital where regular monitoring of plasma lithium levels can be conducted.

The dosage of Camcolit should be adjusted to produce a plasma lithium level between 0.6 and 1.2 mmol/l. The required plasma lithium level may be achieved in one of two ways, but whichever is adopted regular estimations must be carried out to ensure maintenance of levels within the therapeutic range. For consistent results it is essential that the blood samples for plasma lithium estimations are taken 12 hours after the last dose of lithium.

1. 1,500–2,000 mg of lithium carbonate are administered daily for the first five or seven days. A blood sample for plasma lithium estimation is taken 12 hours after the last dose on the fifth or seventh day, and the dosage of Camcolit is adjusted to keep the plasma lithium level within the therapeutic range.

Subsequently, regular plasma lithium estimations must be carried out and, where necessary, the dosage of Camcolit adjusted accordingly.

The precise initial dose of lithium should be decided in the light of the age and weight of the patient; young patients often require a dose higher than average and elder patient a lower dose.

2. A lithium clearance test is carried out and the initial dosage calculated from the results. Even when the initial dosage is calculated in this way, it is still desirable that plasma lithium levels should be determined at weekly intervals during the first three weeks of treatment, and any necessary adjustments to dosage made as a result of the levels actually obtained.

Most of the above applies in the treatment of hypomania as well as mania, but the patient (if not too ill) can be started on treatment as an outpatient provided that facilities for periodic plasma lithium monitoring are available.

Prophylaxis of recurrent affective disorders (including unipolar mania, unipolar depressions and bipolar manic-depressive illness): Treatment of inpatients can be initiated as described above under 'Treatment of Mania'. If treatment is initiated in outpatients 1,000–1,200 mg of lithium carbonate can be administered daily for the first seven days. A blood sample for plasma lithium estimation is then taken 12 hours after the last dose, and the dosage of Camcolit is adjusted to keep the plasma lithium level within the effective range.

Since lithium can impair thyroid function, it is desirable in patients being treated prophylactically that some screening test of thyroid function, such as the protein-bound iodine test, be carried out at about three-monthly intervals. Many of the initial symptoms of hypothyroidism are similar to symptoms seen in depression, and hence it is difficult to differentiate except by some such screening of thyroid function.

In all cases, plasma lithium levels should be determined frequently and, even when consistent levels have been achieved in prophylaxis, should be monitored at least every 10 weeks.

Contra-indications, warnings, etc The first consideration in lithium therapy is the selection of proper candidates. The second is the physical state of the patient, which must be adequate to handle the lithium ion when it is introduced into the body.

Before administering lithium the clinician must make certain that both the cardiovascular and renal systems are functioning adequately by a careful physical examination, including an ECG if necessary. Lithium is contra-indicated in severe renal disease.

Because lithium can impair thyroid function, it is desirable that some screening test, such as protein-bound iodine, be carried out.

Diuretics reduce lithium clearance, consequently lower doses of lithium may be needed in patients receiving diuretics. Frequent monitoring of the plasma lithium level is essential in these patients. Dosage may need adjustment when there is sodium loss or impaired renal function as in exposure to extreme heat, vomiting, intercurrent infection, or urinary tract infection or disease.

Lithium crosses the placental barrier in animals and has been reported to interfere with fertility, gestation and foetal development in several non-human species.

In 1976, a register of babies born to women receiving lithium for varying times during their pregnancies, revealed that of 150 babies, 18 had malformations, of whom 13 had malformations of the cardiovascular system.

Consequently lithium is contra-indicated in the first trimester.

Should the clinician accept the risk of administering lithium during pregnancy, he should note that there have been cases of women who were previously completely stabilised on lithium, developing lithium intoxication at the time of delivery.

It would seem wise to consider a diagnosis of lithium toxicity in all hypotonic infants born to mothers taking lithium and it is important to ensure adequate fluid and mineral intake during the first few days of life.

Bottle-feeding should be considered for children of women on lithium treatment.

Side-effects: Three kinds of side-effects can occur.

1. Transient and harmless symptoms which usually pass after two, or at the most three weeks of treatment. They include nausea, loose stools, fine tremor of the hands, polyuria and polydipsia.

2. The second type of side-effect is also harmless but inconvenient in that it tends to persist. It also includes fine tremor of the hands, polyuria and polydipsia, but weight gain and oedema may also occur.

Some studies suggest that the tremor can be controlled by relatively small doses of propranolol.

3. The third type comprises a group of severe reactions which indicate impending intoxication. It includes vomiting, diarrhoea, coarse tremor of the hands (which can be easily distinguished from the fine tremor seen as a harmless side-effect), sluggishness and sleepiness, vertigo and dysarthria.

Development of goitre and sometimes hypothyroidism are infrequent complications of lithium therapy and it has been suggested that lithium acts only as a triggering agent for latent hypothyroidism in predisposed patients. These are easily controlled by administration of small doses of thyroxine (0.05–0.2 mg daily) concomitantly with lithium.

Pharmaceutical precautions Store in a cool dry place.

Legal category POM.

Package quantities *Camcolit 250:* 100 and 1,000 tablets.

Camcolit 400: 100 and 500 tablets.

Further information The Authors of a recent comparison between Camcolit and two types of 'slow-release' or 'controlled-release' lithium concluded that there was no significant difference in humans in the rate of absorption or excretion of the different products.

A second study demonstrated that patients who had been receiving their daily dose of lithium carbonate in the form of a 'controlled-release' preparation could be changed to the same daily dose of lithium carbonate in the form of Camcolit 400 without significant change in plasma lithium levels or clinical condition.

Product licence numbers
Camcolit 250 0322/5000
Camcolit 400 0322/5015

PRODUCTS ON THE UK MARKET CONTAINING LITHIUM CARBONATE

WITH INDICATIONS

	0108/0035 Phasal tabs 300 mg sustained release	0357/5000 Priadel tabs 400 mg sustained release	0332/0015, 5900 Camcolit 400, 250 tablets 400 mg, 200 mg.
1. Indications	1. treatment at acute manic or hypomanic episodes 2. prophylaxis against relapse in manic depressive disorders recurrent mania, or recurrent depression.	1. treatment of manic, hypomanic and depressive episodes 2. prophylaxis against relapse in recurrent mania, manic depressive illness and recurrent depression.	1. treatment and 2. prophylaxis of mania, manic depressive illness and recurrent depression.
2. Dose			
Acute mania	initially 600 mg bd increase by 300-600 mg /day if no response. Reduce dose once attack has subsided.	higher than normal doses necessary.	to be initiated in hospital 1500-2000 mg for 5 to 7 days, and adjusted after samples taken on 5th/ 7th day.
prophylaxis	600-1200 mg tabs/day in 1 or 2 doses. initially 600 mg in one dose.	1200-1600 mg as a single dose in morning or on retiring.	1000-1200 mg for 7 days, take a blood sample and adjust dose.
Children dose	not recommended		
3. Therapeutic blood levels	0.6 - 1.5 mEq/L do not exceed 2mEq/L	0.6 - 1.5 mEq/L	0.6 - 1.2 mEq/L
4. Contraindication			
renal disease	significant renal disease.	severe renal disease.	in severe renal disease.
cardiovascular disease	significant cardoivascular disease.	severe cardiovascular disease.	
hypothyroidism	hypothyroidism	frank hypothyroidism	
Addison's disease		Addison's disease	
sodium balance disorders	sodium depletion, or conditions requiring low sodium intake.		
5. Precautions			
pregnancy	not to be used in pregnancy unless alternative therapies have proved unsuccessful, and the physician considers that the benefits outweight the risk.	treatment to be discontinued as a general rule during planned or confirmed pregnancy - Li is secreted in breast milk. Babies may show signs of Li	contra-indicated in 1st trimester. Important to ensure adequate fluid and mineral intake in all hypothermic babies [illegible] mothers on

	PHASAL	PRIADEL	CAMCOLIT
	Blood levels to be monitored.	toxicity, and need fluid therapy as neoates.	Li. Bottle for ng should be consi red.
6. eldery patients	Use more cautiously as renal lithium clearance may be reduced.	recommended that starting dose is 800 mg (also if patient under 50 kg).	
7. Drug interactions			
diuretics	not to be used.	concurrent use contra-indicated.	lower doses of diuretics may be needed as diuretics reduce Li clearance. Frequent monitoring of patients essential
antidepressants	Li does not cause addiction or tolerance it maybe considered with the usual anti manic or antidepressive treatments.	all currently known antidepressant and anti manic drugs (including ECT) are compatible c priadel.	
diet	maintain a normal diet with adquate salt and fluid intake.	caution should be exercised to ensure that diet and fluid intake are normal, thus upholding a normal electrolyte balance.	

8 Side effects and warnings	0100/0035 Phasal tabs 300 mg S-R	0357/5000 Prindel tabs 400 mg S-R	0332/0015, 5900 Camcolit 400, 250 tabs 400 mg 250 mg
(i) pre-treatment examination	pre-treatment laboratory and physical examination is required, and should be repeated periodically	estimate serium Li levels to check whether patients are receiving Li in any other form. A creatinine clearance test should be performed if necessary	dinician to assess cardiac and renal function, including ECG if necessary. Lithium renal clearance test necessary
(ii) Frequancy of blood sample monitoring.	measure blood levels weekly until stablized, and then weekly for the month after stabization, and then month monthly.	1st sample 4/5 days after starting treatment and weekly thereafter until stabilzation acheived, estimations thereafter should not exceed 3 months.	determine weekly for 1st 3 weeks in acute mania. Li levels should be monitored at least 10 - weekly when stablizied.
(iii) blood levels to be taken:-	(a) on changing Li preparations (b) on appearance of prodromel toxic signs, dosage alteration development of significant intercurrent disease, signs of manic or depressive relapse, change in Na or fluid intake, or during pregnancy and parturition.	when changing from other Li preparations. Daily dose to be as close as possible to other form of lithium. During pregnancy at signs of side-effects.	
maximum blood levels occur -	within 2-4 hours of dosing.		
(iv) blood samples to be taken -		before daily dose.	12 hours after last dose.
Thyroid function		thyroid function tests approximately once yearly. Hypothyroidism can be treated with concurrent thyroxine.	thyroid function should be screened 3 monthly on prophylactic doses, as symptoms of depression are similar to those if early hypothyroidism. Li can impair thyroid function concurrent thyroxine can be used.

	PHASAL	PRIADEL	CAMCOLIT
adjust or reduce doses in cases of:-	early signs of toxicity.		sodium loss, impaired renal function as in exposure to extreme heat, vomiting, intercurrent infection, urinarytract infection or disease.
(v) stop treatment in case of:-	intoxication, such as appearance or aggravation of drowsiness, lethargy, coarse tremor, anoresia, vomiting and diarrhoea. (See also effects).	intercurrent renal infection; only to be re-instituted when kidney function is normal again also at signs of intoxication.	
transient side effect	infrequent below 1.5 mEq/L, mild g-i effects, nausea, vertigo, muscle weakness and a daze feeling.	unlikely below 2mEq/L fine hand tremor, mild polydipsia, mild polyuria, initial anorexia, some losening of stools more rarely mausea and diarrhoea.	mausea, loose stools fine tremor, polyuria and polypipsia.
persisent side-effects	fine hand tremor, polyuria mild thirst, oedema and non-toxic goitre have occurred after prolonged treatment.	weight gain and oedema may present in some patients.	find hand tremor, polyuria, and polydipsia weight gain and oedema may occur.
level of side effect and intoxication	aggravation of g-i effects, muscular weakness, lack of coordination, drowsiness, lethargy, increasing toxicity atoxia, giddiness, tinnitus blurred vision, coarse tremor, muscle hyperirribility and polyuria. At 2-3 mEq/L increasing disorientation, coma and death.	increasing anorexia, vomiting and diarrhoea. Also mild drowsiness and sluggishness increasing to giddiness with atoxia, coarse tremor, tinnitus, blurred vision, muscular twitching, dysarthria progressing at 2-3 mEq/L to seizures coma and death.	vomiting, diarrheoa, coarse hand tremor, sluggishness, sleepiness, vertigo and dysarthria.

from our files

RECENT DEVELOPMENTS WITH LITHIUM

☐ Clinical studies update

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From our files

LITHIUM (continued)

☐ Views and reviews

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SIDE-EFFECTS OF LITHIUM

☐ Update on Kidney Damage

At a recent meeting of the Scandinavian Society for Psychopharmacology, 3 more reports were made on impaired kidney function and biopsy-confirmed renal pathology in patients on lithium. The data were preliminary but they indicate a 15-20% incidence of renal pathology in patients treated with lithium. As the kidney lesions progress slowly there is little risk that terminal azotaemia would develop. Because of decreased urine concentrating ability, however, there is an increased risk of dehydration and lithium intoxication. Patients who become polyuric must therefore be advised to drink plenty of fluids. Periodic renal function tests are recommended for all lithium-treated patients. All valuable drugs may do harm as well as good. Although physicians must protect patients from the adverse effects of medicines, they must also protect them against the ravages of untreated or inappropriately treated illness. This entails weighing the risks of treatment against the harm of no treatment.

'Lithium is too valuable a drug to be abandoned at this stage of our knowledge of its potential adverse effects . . . The best service we can provide patients is to master the art of lithium therapy; not to succumb to the expediency of rejecting a therapy that has and still can benefit untold victims of affective disorders, their families and society,' advises the editor of the International Drug Therapy Newsletter.

International Drug Therapy Newsletter 13: 17 (May 1978) (Inpharma 13 May 1978 p2)

☐ And Long-Term Treatment May Impair Renal Concentrating Capacity

Long-term (2 months to 11 years) treatment of 60 patients with lithium resulted in impaired renal concentrating capacity compared with 30 healthy subjects. Nineteen of the 60 had been treated with lithium alone and 41 in combination with neuroleptic drugs. Renal concentrating capacity was impaired in 25 subjects who had received neuroleptic drugs alone. Two months after lithium was withdrawn renal concentrating capacity improved more in patients who had received lithium alone than in those who had lithium combined with neuroleptic drugs. As total lithium dose increased, osmolarity decreased, and was impaired in all 13 patients who had received more than 600 g of lithium.

Shannon, C.A. et al. Lancet 1: 775 (8 Apr 1978)

LONG TERM LITHIUM — SHOULD CRITERIA FOR ITS USE BE STRICTLY FIXED?

A study of kidney structure and function in patients on lithium for affective illness has shown reduced concentrating capacity and a unique tubular lesion in biopsy specimens from 5 patients who had been on the drug for 4 and 5 months and 6, 7 and 9 years. This lesion was mainly in distal convoluted tubules and collecting ducts, with proximal tubules showing only minor changes. The most obvious feature was ballooning of cells and vacuolation of cytoplasm, but the additional changes were different from any previously described tubular changes. Three patients who had taken lithium for 6, 7 and 9 years had more advanced changes of the type previously described, including sclerosis of 10-20% of glomeruli, tubular atrophy and interstitial fibrosis. The finding of only tubular changes in early biopsy specimens and of focal nephron atrophy in later ones suggests that the tubular lesion may lead to the focal nephron atrophy seen after prolonged lithium treatment. Serum creatinine and urea were normal in all 5 patients and there were no excess red blood cells or protein in urine, so the usual indications for biopsy were absent.

This and other reports 'suggest that criteria for using lithium for long term treatment must become stricter'. If long-term prevention of unipolar depressive episodes with continuous tricyclic drugs does not cause kidney lesions, then if there are no cardiac problems, 'tricyclics may be the treatment of choice for recurring depression while lithium is reserved for bipolar patients'.

Barrows, G.D. et al.: Lancet 1: 1310 (17 Jun 1978) (Inpharma 1st July 1978, p4.

LITHIUM INTOXICATION IS A SERIOUS CONDITION

. . . Control of Serum Levels and Regular Renal Assessment Are Recommended to Prevent It

Lithium intoxication was studied in 23 patients, 21 of whom developed intoxication while on a maintenance dosage that had been unchanged for 2 months-12 years. One developed intoxication after only 6 days' treatment and 1 had taken an overdose. Lithium intoxication developed gradually in most patients and was characterised by mental and neurological symptoms. Only 2 patients had gastrointestinal symptoms. There were toxic effects on brain, heart and kidneys. The severity of intoxication seemed to depend on at least 3 factors: serum lithium concentration, length of intoxication and individual tolerance. Intoxication was preceded by disorders of water and electrolyte metabolism in most cases, and water loss due to impaired renal concentrating ability seemed to be a major predisposing factor. 17 patients had renal insufficiency on admission and normal renal function did not return in 5. Renal biopsy in 7 patients showed abnormalities suggesting that a chronic nephropathy, possibly caused by lithium, might also be a predisposing factor.

Sodium chloride infusion did not specifically affect lithium excretion. As some patients developed hypernatraemia, it is not recommended. Haemodialysis is at present the most effective method for removing lithium from intoxicated patients. It should be continued for long enough to attain a lithium concentration below 1 mmol/L after redistribution of lithium in the body. Peritoneal dialysis should be used only when haemodialysis is not possible. Of the 23 patients, 2 died and 2 developed persisting neurological sequelae. Lithium intoxication can best be prevented by control of serum levels and regular assessment of renal function and renal concentrating ability during treatment.

Hansen, H.E. and Amdisen, A.: Quarterly Journal of Medicine 47: 123 (Apr 1978)

BK

COMMITTEE ON REVIEW OF MEDICINES

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

PHARMACEUTICAL RECOMMENDATION

LITHIUM CARBONATE

[redacted]

Legal Status

Lithium Carbonate is available on prescription only except where the maximum dose is the equivalent of 5mg of the base or less and the maximum daily dose is 15mg of the base or less.

SUB-COMMITTEE ON PSYCHOTROPIC AGENTS

Ingredient No: A 1926

Date of Meeting: October 1978

Medical Assessment: [redacted]

Pharmaceutical Assessment: [redacted]

REPORT ON LITHIUM CARBONATE

1. INTRODUCTION

1.1 Formula

$Li_2 CO_3$

Lithium Carbonate

1.2 Description

A white, crystalline powder; odourless; taste, slightly alkaline.

1.3 Background

Lithium was discovered in 1817 and named after the stone from which it was extracted ("lithos" - Greek). It occurs in many minerals, plant and human tissues although no biochemical or physioligical system is shown to need it.

It was a popular remedy in the 1850's for gout, renal calculi and rheumatism, and in the 1920's as an epileptic, a tonic and hypnotic. In the 1940's, Lithium chloride was introduced as a salt substitute but was withdrawn after toxicity cases were reported, especially in those with heart or kidney disease.

The efficacy of Lithium carbonate in mania was first discovered in 1949, and confirmed only in 1968.

1.4 Pharmacopoeal Entries

Lithium carbonate BP., also FR, Swiss and USP.

Lithium carbonate BP., also USP.

Slow Lithium carbonate tables BP.

Lithium carbonate capsules USP.

1.5 Pharmacopoeal Dose

Up to 1.6g daily, in single or divided doses; subsequent doses in accordance with the plasma concentration of lithium.

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1.6 Pharmacopoeal Indications

Used in theprophylaxis and treatment of manic-depressive disorders.

1.7 Legal Status

Lithium carbonate is avilable on prescription only.

An amendment to the Medicines (Prescription only) Order 1977 (SI 1977 No 2127) has been agreed in respect of Lithium carbonate ie products containing Lithium carbonate will be exempt from the class of prescription only medicines where the maximum dose is the equivalent of 5 mg of base or less and the maximum daily dose is 15 mg of base or less. (cf Lithium sulphate).

Products on the UK Market

There are 12 products on the UK market containing lithium carbonate, 5 of these, detailed below, contain lithium carbonate as the only active ingredient and are all promoted for use in the prophylaxis and treatment of manic-depressive disorders.

PL 0108/0035 (Pharmax)	Phasal tablets	300mg	Sustained release
PL 0332/0015	Camcolit 400 tablets	400mg	
PL 0332/5900 (Norgine)	Camcolit 250 tablets	250mg	
PL 0357/5000 (Delandale Labs)	Priadel tablets	400mg	Sustained release
PRL 0912/5892 (Woodward)	Lithium carbonate tablets BP	250mg	

The remaining 7 products contain smaller quanitites of lithium carbonate in combination with several other ingredients.

PLR 711/5005	Gout Varalettes	62.4mg Li_2CO_3 /unit dose
PLR 209/5006	Diuromil	0.39% Li_2CO_3 (cancelled)
PLR 711/5003	Granular Effervescent Citrate of Lithia	3.162% Li_2CO_3
PLR 711/5006	Urobishop	0.3% Li_2CO_3
PLR 711/5008	Carlsbad Salt	0.37% Li_2CO_3
PLR 2269/5007	Rehabiliation Bath AHP	1.2% Li_2CO_3
PLR 2269/5010	Bromine-Valerian Bath AHP,	level of Li_2CO_3 not stated.

HS

PHARMACEUTICAL REPORT ON LITHIUM CARBONATE

Only the five products promoted as psychotropics are discussed.

Background

A specification for Lithium carbonate was included in the BPC 1949; a psychotropic use was not listed. The dose was 0.12-0.3g.

Lithium carbonate for use in the prophylaxis and treatment of manic-depressive disorders at a dose of up to 1.6g daily, first appeared in the BP addendum 1969. The BPmonograph was developed in consultation with Camden Chemical Co. Ltd.

[redacted]

Availability of Lithium carbonate from oral preparations

There are five products on the market containing Lithium carbonate only; four are proprietary preparations, two of which claim slow-release properties, one controlled release and one generic, Lithium carbonate tablets BP 250mg.

The dissolution pattern for slow Lithium carbonate tablets specified in the current BP is:-

2h not more than 30%

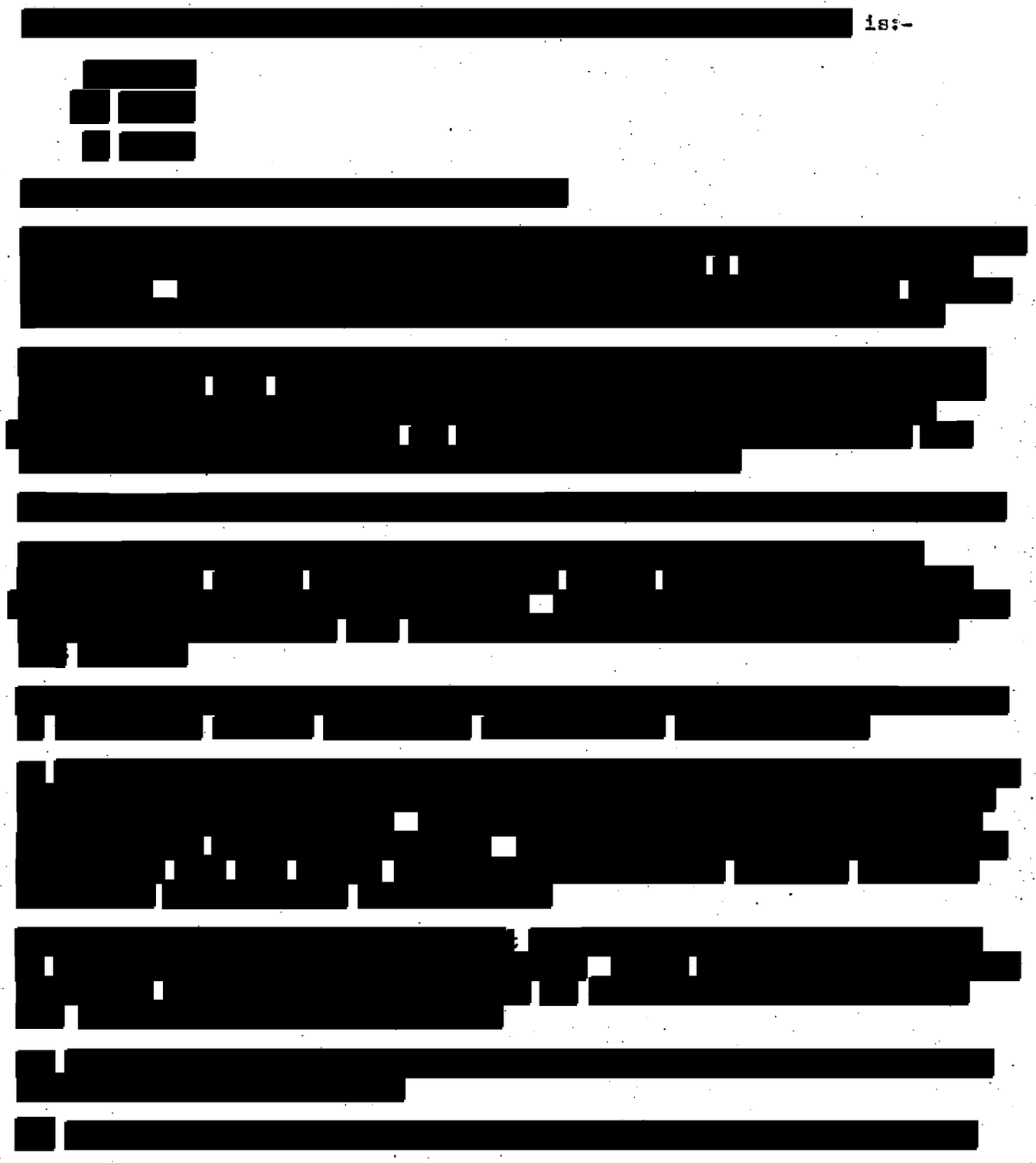
3h not less than 30% and not more than 50%

5h not less than 70% and not more than 95%

31

[redacted] is:-

[redacted]



Bioavailability

The pharmacokinetics of Lithium are most easily related to partial ion substitution. Lithium salts are efficiently absorbed from the gastro-intestinal tract with peak and plateau serum concentrations in 30 minutes and 12-14 respectively (7). However, Lithium crosses cell boundaries at a relatively slow rate with a distribution volume equal to body water. This slow entry into and exit from

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the intracellular space accounts for the delay of 6-10 days in achieving the full therapeutic response to Lithium and for the delay in excretion when Lithium is discontinued.

The proprietary preparations contain different amounts of Lithium carbonate and recommend different dosage regimens (see Appendix II).

Preparations containing Lithium carbonate do not appear to be bioequivalent. This problem of the bioavailability of lithium from formulations containing Lithium carbonate has been widely reported and discussed. This has publicised the problem but nothing has, as yet, been done to resolve it.

In vivo studies showed that after a single dose of Camcolit (400), Priadel and Phasal similar plasma levels were found after Priadel and Camcolit but lower and more variable levels after Phasal (8). There appears to be a tendency for slightly lower serum levels on Phasal which might require a slight increase in dosage.

The interchangeability of Priadel and Camcolit 400 when Camcolit 400 was substituted in patients who were already stabilised on Priadel has been demonstrated. (In house data).

Camcolit 400 appears to be bioequivalent to Priadel.

Whilst both 'Phasal' and 'Priadel' claim slow release characteristics they are not generally reported to be bioequivalent. Apparent bioequivalence of the two products in a small trial of 18 schizophrenic patients is reported (9). Doses were given once daily at 7.0pm or 8.0am. 'Priadel' tended to give a higher peak in serum concentration of Lithium than 'Phasal' in the early period after drug administration. When the preparations were taken at night the serum concentrations of Lithium were not significantly different in the main waking hours of the day up to and including 6.0pm. The two preparations appeared to be bioequivalent in this study. For a once-a-day administration it is better to give sustained release forms of Lithium salts at night so that any peaks in serum concentration occur during sleep, but twice-a-day dosage is preferable.

Other studies have shown that 'Phasal' gives serum levels of 0.72 ± 0.02 m eq/l in stabilised subjects. (Unpublised results).

Plasma levels were compared in healthy volunteers after taking 'Camcolit'400 or 'Camcolit' 250. Peak plasma levels after 'Camcolit' 400 were generally lower than after Camcolit 250. (In-house data). Whilst the company do not claim Camcolit 400 as a slow release preparation it is formulated in such a way that the release is controlled or optimised in order to avoid dangerously high peak levels when used by those physicians who prefer to give Lithium on a once daily dosage regimen.

In an, as yet unpublished investigation, Camcolit 250 was used in a once daily dosage regimen. Plasma levels over 24h were very variable therefore once daily dosage with Camcolit 250 is not recommended.

Some control over the release of Lithium carbonate seems to have been achieved with Camcolit 400.

Dosage of Lithium must be adjusted in the individual patient according to clinical conditions and the results of regular serum lithium determinations (range 0.6-1.5m Eq/l : not to exceed 2m Eq/l) therefore bioequivalence of products is important.

Comment

[redacted]

3. Companies should be asked whether they would allow information on the five products specified to be exchanged between the CRM Secretariat and the BP Commission.

4. In Lithium carbonate therapy serum drug levels are done routinely. It is possible that the complete lack of uniformity of the products containing Lithium carbonate is a contributory factor to this requirement.

5. The CRM should be asked whether the non-uniformity of the products, the variable dissolution patterns and bioinequivalence constitute a possible clinical hazard.?

Prescribing figures for products containing Lithium Carbonate

The data have been extracted from a statistical analysis of all prescriptions in Great Britain in 1976

Prescribing name	Number of prescriptions (thousands)	Type of prescription
Priadel (400 mg)	94.2	Proprietary
Phasal (300 mg)	2.8	"
Camcolit 250	16.1	"
Lithium carbonate 400mg	6.6	Non-proprietary
Lithium carbonate 300mg	0.2	(Prescriptions generic but only available as a proprietary)
Lithium carbonate 250mg	28.3	

Comments

1. Figures for Camcolit 400 are not included as the licence for this product was only granted 2.3.77.

2. Generic prescriptions do not appear to specify slow release characteristics for a product. The products must therefore be identified by tablet strength only.

3. Slow Lithium Carbonate tablets BP do not appear to be prescribed as such.

Comparison of specifications for Lithium Carbonate

[redacted]

APPENDIX II

Comparison of dosage and dissolution characteristics of products containing Lithium carbonate.

[redacted]

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after administration of yambolap but uptake increased significantly during exercise, in accord with the animal experiments. At rest the V_E fell but the oxygen percentage of the expired gas was not much altered.

Oxygen uptake increased as exercise performance increased. However, comparison of the $\dot{V}O_2$ values at the same load before and after yambolap administration, revealed a relative decrease. The drug seemed to produce, in every patient, striking changes in exercise tolerance when compared with the placebo response. The time to total recovery became shorter, and the ratio of exercise-time and recovery-time rose significantly, pointing to a better ability of regeneration. The duration of anginal pain was also shorter. The oxygen debt formed after the exercise, was also decreased significantly. Yambolap produced a remarkable reduction in the S-T segment depression compared with the placebo response.

We think that this drug might be effective in angina pectoris. It probably acts by influencing energy utilisation at a subcellular level, and in this respect would not be comparable to beta-blockers or nitrates.

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LIMITATIONS OF COMMERCIAL TEST FOR ANTIBODY TO HEPATITIS A VIRUS

SIR,—During a prospective study on consecutive cases of acute viral hepatitis a commercial test ('HAVAB', Abbott) for antibody to hepatitis A virus (HAAb) was evaluated.

Specimens with high IgM but low IgG titre[1] gave low titres which were not reduced after cleavage of IgM antibodies with 2-mercaptoethanol[2] (see table). High titres were obtained with specimens with high IgG titres, which, however, demonstrated lower sensitivity of the Abbott test. Thus the test measures IgG, not IgM, and the manufacturers have confirmed this.

HAAb TITRES BY FLEHMIG AND ABBOTT RADIOIMMUNOASSAYS IN ACUTE AND CONVALESCENT SERA FROM TWO PATIENTS (A AND B) WITH HEPATITIS A

Serum	HAAb titre		
	Flehmig[1]		Abbott (before/after 2-M.E.)†
	IgM	IgG	
A: acute (day 15)	319 000	2600	40/20
A: convalescent (day 96)	100 000	32 000	80/160
B: acute (day 7)	600 000	7500	20/10
B: convalescent (day 107)	80 000	67 000	640/640
Control*	53 000	150	1/<1

*IgM positive; IgG almost negative.
†2-mercaptoethanol treatment.

(The HAVAB test does demonstrate fractionated HAAb IgM, but fractionation is not included in our routine diagnostic work.) It might be possible to demonstrate a significant increase in IgG titre between acute and convalescent serum. Abbott recommends titration in duplicate. However, titration in two-fold dilutions from 1:50 to 1:3200 would need twenty-eight beads; at 12·75 crowns per bead the cost per patient in Sweden would be 357 crowns (about £40) merely for beads.

Abbott states that inverse proportionality is achieved between amount of HAAb and counts/min within an appropriate range of concentration. However, we found this range to be too narrow to allow for determination of the titre by interpolation of a single c.p.m., particularly if obtained on an undiluted specimen, within a standard curve. Thus most undiluted serum specimens, positive in the test, reduced the c.p.m. of the standard ^{125}I-HAAb to the same extent as did the positive control HAAb.

The Abbott HAVAB test can be used for studies of immunity but needs modification for diagnostic use.

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LITHIUM-INDUCED URÆMIA

SIR,—The nephrotoxic effects of lithium have been known for many years, but the finding that regular treatment may cause renal damage is alarming. In an earlier series[1] we found only moderately reduced renal function in 7 out of 14 patients. In a screening investigation (unpublished) 8 out of 110 patients treated with lithium for more than 6 months had signs of reduced renal function with a highest serum-creatinine of 2·2 mg/dl. We report here a case of probable lithium-induced uræmia in a patient on regular lithium treatment for only 3 years.

The patient is a 54-year-old man. In 1960 he had an isolated incident of nephrolithiasis. From 1964 he had several depressive episodes and treated with antidepressive drugs for the next 10 years. He was put on lithium in 1974, and from 1974 to 1977 lithium sulphate was his only drug. Renal function and blood-pressure had been normal and there had been no proteinuria in 1972, 1974, or 1976. During lithium treatment he had daily urine volumes of 3–4 litres, but in the summer of 1977 urine volumes up to 8–10 litres were recorded. The serum lithium was measured every 1–2 months. Once, in December, 1975, it was 1·4 mmol/l, but every other routine measurement was below 1·1 mmol/l. When serum-lithium was measured in September, 1977, because of symptoms of tiredness and increasing urine volumes, the value was 2·1 mmol/l, although the same lithium dose had been administered all the time (lithium sulphate 3·3 g/day [60 mmol/day]). Lithium was stopped for a few days and the lithium concentration rapidly fell. Treatment was then continued at a lower dose (1·7 g/day). In all measurements thereafter serum-lithium was below 1·0 mmol/l. Lithium treatment was stopped in December, 1977, when signs of renal damage were observed. In November, 1977, serum-creatinine was 152 µmol/l, and increased rapidly up to 500 µmol/l late in February, 1978. The glomerular filtration-rate decreased between January and March from 38 to 13 ml/min. Thereafter, the renal function, last measured in November, 1978, has been stable. The blood-pressure was slightly raised in September, 1977, and from November, 1977 he was put on antihypertensive treatment. When admitted in February, 1978, for kidney biopsy he had a slight anæmia, E.S.R. 46 mm/h, and proteinuria of 1 g/day, but no hæmaturia. On X-ray the kidneys appeared to be of normal size; there were no calcifications, no urinary-tract obstructions, but the charging was reported to be decreased.

Renal biopsy revealed severe focal interstitial cortical fibrosis and nephronic atrophy. With our "point count" technique[1] we found 38·4% interstitial fibrous cortical tissue. 4 out

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of 18 glomerular sections were totally sclerotic. In the rest of the glomeruli there were no specific changes such as hypercellularity, adherences, crescents, or any other evidence of glomerulonephritis. In the fibrous scars there were atrophic tubular profiles and a focal moderate mononuclear cell inflammation. There was a moderate arteriolosclerosis. The medulla was not represented. immunefluorescence investigation of IgG, IgA, IgM, complement C_3, C_4, properdin, fibrinogen, and properdin A were negative in the glomeruli, but there was an increased amount of C_3 in the interstitium and in the tubular basement membranes.

The clinical picture, with alarming signs of rapidly developing renal insufficiency, and the biopsy findings clearly point to a nephrotoxic disease. The histological picture is very similar to our previously published[1] and unpublished findings from two groups each of 14 patients on long-term lithium. This chronic interstitial nephropathy is unspecific, but there were no symptoms or signs of other causes of nephropathy. The patient's first symptoms of a renal disease were increasing polyuria, a well-known side-effect of lithium. We also consider it significant that the rapid progression of renal insufficiency stopped when lithium treatment was withdrawn. There have been no signs of activity of the disease during the past 8 months. The similarity of the histological picture to our published description of renal lesions in patients on long-term lithium treatment clearly points to lithium as the causative agent. Lithium treatment, even when well controlled, may cause severe renal damage; our patient was on the brink of dialysis treatment before the diagnosis was made.

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LOCAL SNARES IN CORONARY SURGERY

SIR,—The use of the encircling tapes or snares to control blood-flow from the opened right coronary artery during aortocoronary bypass surgery remains quite common,[1] despite the introduction of cardioplegic arrest[2] which should obviate the need for such local control. A local snare has the potential for promoting obstruction and occlusion from plaque fracture or subintimal hæmorrhage and this danger should be worst with the distal right coronary artery, which is usually heavily and diffusely arteriosclerotic and often calcified. Figs. 1 and 2 illustrate just such a case of iatrogenic occlusion so that an otherwise excellent operation technically (the graft being patent at both ends) is rendered useless.

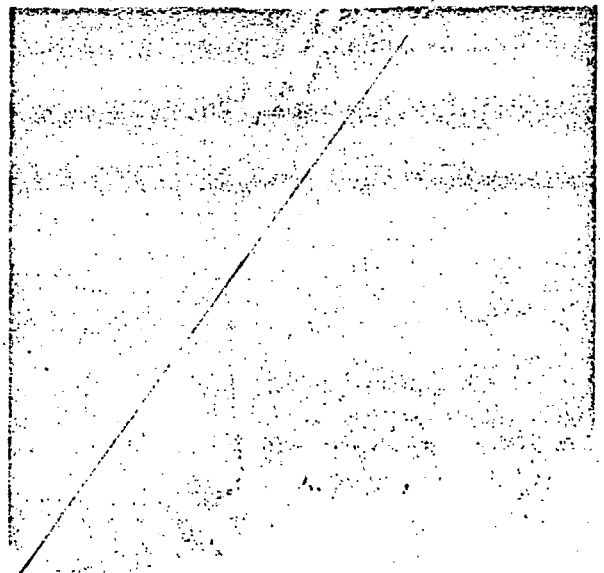

Fig. 1—Preoperative angiogram shows tight proximal occlusion of right coronary artery with no significant distal narrowing.

Fig. 2—One month postoperatively distal artery is totally occluded (large arrow) just beyond distal anastomosis.
Graft perfectly patent at both ends. Dye injected into native right coronary flows back up graft into aorta (small arrows indicate direction of flow).

This case is not unique, as I have learned from other surgeons, and I believe it is time to condemn the use of local snares in coronary surgery. For those who remain uncomfortable with the use of anoxic arrest, a better technique to control local bleeding is to insert a small balloon-tipped embolectomy catheter attached to a three-way stopcock. The balloon is then inflated to precisely the point at which bleeding stops, and a turn of the stopcock maintains this position. Intraluminal control such as this is far less likely to damage the arterial wall than external crushing with a snare.

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FALSE-POSITIVE PARACETAMOL ASSAY

SIR,—A potential source for false-positive results in the colorimetric plasma-paracetamol method of Glynn and Kendall[1] was uncovered when the remaining contents of a syringe of arterial blood on which a blood-gas assay had just been done were centrifuged to provide plasma for a paracetamol assay. The plasma gave an apparent positive result. Venous blood from the same patient was negative. These findings were confirmed by repeating the tests on the same samples. The arterial sample had been taken into a syringe previously heparinised with a small volume of 25 000 I.U./ml heparin injection (mucous) *B.P.* containing 0·3% v/v cresol (Paines and Byrne) while the venous sample had been put into a lithium heparin tube (Searle).

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Renal function after long-term treatment with lithium

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British Medical Journal, 1979, **1**, 1457-1459

Summary and conclusions

Daily urine volumes, plasma creatinine concentrations, and creatinine clearance were measured in 106 patients with unipolar and bipolar affective disorders attending a "lithium" clinic. Urine volumes exceeded 3·5 l in only six patients, plasma creatinine concentrations exceeded 150 μmol l (1·7 mg 100 ml) in only five, and creatinine clearance was below 50 ml/min in 16. Renal function was assessed by measuring creatinine clearance and renal tubular function, including response to 20 hours of water deprivation, in a representative sample of 30 patients from the lithium clinic and 30 psychiatric patients matched for age and sex who were taking other psychotropic drugs. Creatinine clearance and tubular function, including urine osmolality after water deprivation, were not significantly different between the two groups. Urinary excretion of arginine vasopressin (AVP), however, was much greater in the lithium-treated patients, who therefore had a diminished tubular responsiveness to AVP.

The findings do not support suggestions that long-term lithium treatment results in seriously impaired renal function, renal damage, and polyuria. Compared with other series, however, the patients were being maintained with low serum lithium concentrations, which apparently are as effective prophylactically as higher concentrations.

Introduction

Long-term treatment with lithium may cause polyuria[1] associated with an increase in plasma antidiuretic hormone (ADH),[2] and it is therefore due wholly or largely to diminished renal responsiveness to ADH. The polyuria is troublesome but not serious. Recent reports, however, suggest that lithium reduces the glomerular filtration rate and causes a focal interstitial nephropathy.[3] Such reports cast doubt on the future use of lithium in the long-term treatment of recurrent affective disorders.

We have measured the daily urine volumes and creatinine clearance in 106 patients attending our "lithium" clinic. Thirty of these patients and 30 patients matched for age and sex who were taking other psychotropic drugs were admitted overnight and investigated for ergatinine clearance and several renal tubular functions, including urine osmolality after water deprivation.

Patients and methods

Table I gives the details of 123 patients attending the clinic. All were asked to collect urine for 24 hours, ending at 0800 on the day of their next routine visit. Verbal and written instructions on how to collect the urine had been given to each patient at the previous visit. Only 24-hour collections containing over 80% of the daily lithium dose were accepted as complete. If the collection contained less than this it was repeated once after further instructions and explanations. A total of 106 patients produced a satisfactory collection.

TABLE I—*Details of 123 patients attending lithium clinic*

	Age (years)		Duration of lithium treatment (months)	Serum lithium concentration 12 hours after last dose (mmol l)	Dosage of lithium carbonate (mg)
	Men (n = 39)	Women (n = 84)			
Mean ± SD	55·6 ± 13·7	54·2 ± 12·9	74·1 ± 38·8	0·59 ± 0·17	802·5 ± 290·0
Range	21-81	19-77	6-180	0·31-1·07	250-2000

Conversion: SI to traditional units—Serum lithium: 1 mmol l = 0·7 mg 100 ml.

We selected as a representative sample 30 patients who had been taking lithium for a mean of 8·3 ± SD 2·8 years (range 3·0-12·4 years) and 30 psychiatric patients matched for age and sex with the lithium group who were taking psychotropic drugs other than lithium. Patients and controls were admitted in random order to the research unit and stayed from 1800 till 1500 the next day. Subjects took no medication from 18 hours before admission until the end of the test except for 5 mg nitrazepam on retiring to bed. Throughout their stay patients were supervised by the nursing staff of the unit who ensured that they took no food or drink and that all urine was collected. The patients were accurately weighed at 1900, 0700, and 1500. Blood samples were taken, without stasis, at 0900 and 1400 into strontium-heparin tubes, which were stoppered so that no air was trapped above the blood. Urine was collected over 18 hours from 1900 to 1300 and used to measure creatinine clearance. A further, two-hour urine sample, collected between 1300 and 1500, was used to assess tubular function.

Plasma sodium, potassium, calcium, and bicarbonate concentrations and plasma and urine creatinine and phosphate concentrations were measured on a Vickers M300 multichannel analyser. Urine osmolality was measured on an advanced osmometer; urine β_2-microglobulin was measured by radioimmunoassay (Phadebas), and arginine vasopressin (AVP) was measured by a specific and sensitive radioimmunoassay.[4] Urine AVP was expressed as osmolar clearance (μg/ml), which is closely related to plasma AVP.

Glomerular function—Creatinine clearance was calculated from creatinine excretion in the 18-hour urine collection and the creatinine concentration in the 0900 plasma sample.

Tubular function—Tubular reabsorption of small-molecular-weight proteins was assessed from the excretion of β_2-microglobulin in urine. The *maximum tubular reabsorption capacity for phosphate per unit* of glomerular filtration rate (GFR) was calculated from the phosphate and creatinine concentrations in plasma and urine.[5] Tubular reabsorption of water was assessed from the 24-hour urine volume in the large group and from the urine osmolality and weight loss after water deprivation for 20 hours in the smaller groups. In the smaller sample the relation between urine AVP and urine osmolality was used to assess tubular responsiveness to AVP.

Results

Only six of the 106 lithium-treated patients had a 24-hour urine volume exceeding 3·5 l, and only five had a plasma creatinine concentration above 150 μmol l (1·7 mg 100 ml); two of these patients had both an increased urine volume and a raised plasma creatinine concentration. The 24-hour creatinine clearances were very variable, 30-40 to 165 ml/min; mean 75·7 ± SD 30·2 ml/min. Thirty-eight patients had a creatinine clearance below 70 ml/min, and in 16 it was below 50 ml/min.

Table II shows the various assessments of renal function in the

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smaller, selected lithium group and controls. The two groups had similar mean plasma creatinine and creatinine clearance values. Many patients in each group had low creatinine clearance values: 10 controls and 16 lithium-treated patients had values below 70 ml/min, and 10 of the controls and 15 patients in the lithium group had clearance values below 50 ml/min. Except for two patients in the lithium group, however, the plasma creatinine concentration was normal in all patients.

TABLE II—*Renal function in lithium-treated and control patients. Values are means ± SD*

	Lithium group (n = 30)	Control group (n = 30)
Urine volume over 18 hours (ml)	1573 ± 169	1209 ± 62
Creatinine clearance (ml/min)	61·1 ± 30·2	81·3 ± 52·0
Plasma creatinine (μmol/l)	93 ± 29	81 ± 15
Phosphate clearance (ml/min)	15·6 ± 5·4	17·0 ± 7·9
Phosphate: creatinine clearance ratio	0·29 ± 0·18	0·25 ± 0·15
β_2-microglobulin clearance (μg/l)	213 ± 206	220 ± 200
β_2-microglobulin clearance (μg/h)	11·8 ± 11·4	13·0 ± 14·6
Values after 20 hours of water deprivation:		
Osmolality (mmol/kg)	509 ± 193	579 ± 207
Weight loss over 12 hours (kg)	1·19 ± 0·50	1·27 ± 0·92
Log urine AVP	1·693 ± 0·14	1·098 ± 0·47
Urine AVP (pg/min)	77·7 ± 72·5	21·2 ± 21·5
Urine AVP (pg/ml)	49·3 (18-136 (±1SD); 6·5-374 (±2SD))	12·5 (3·3-37 (±1SD); 1·4-109 (±2SD))

Conversion: SI to traditional units—Plasma creatinine: 1 μmol/l = 0·01 mg/100 ml. Osmolality: 1 mmol/kg = 1 mosmol/kg.

Urinary excretion of β_2-microglobulin and tubular reabsorption of phosphate were similar in the two groups, as was the weight loss during water deprivation and the urine osmolality at the end of water deprivation. Urinary excretion of AVP, however, was much greater in the lithium-treated group.

Table III gives the plasma electrolyte, urea, and creatinine concentrations after water deprivation in the two groups. No significant differences were observed.

TABLE III—*Mean plasma values ± SD after 20 hours of water deprivation in lithium-treated and control patients*

	Lithium group (n = 30)	Control group (n = 30)
Sodium (mmol/l)	141·4 ± 3·6	140·0 ± 3·2
Potassium (mmol/l)	4·19 ± 0·24	4·08 ± 0·37
Calcium (mmol/l)	2·65 ± 0·16	2·61 ± 0·11
Bicarbonate (mmol/l)	23·9 ± 1·9	26·8 ± 3·3
Urea (mmol/l)	4·97 ± 1·17	4·71 ± 1·17
Creatinine (μmol/l)	92·8 ± 25·8	83·8 ± 15·3

Conversion: SI to traditional units—Plasma sodium, potassium, and bicarbonate: 1 mmol/l = 1 mEq/l. Plasma calcium: 1 mmol/l = 4·0 mg/100 ml. Plasma urea: 1 mmol/l = 6·0 mg/100 ml. Plasma creatinine: 1 μmol/l = 0·01 mg/100 ml.

Discussion

Of the 106 patients receiving long-term lithium treatment, only six had polyuria, and detailed study showed that as a group they could increase their urine osmolality as much as the controls during water deprivation. Urinary AVP in the lithium group, however, was higher for any urine osmolality than in the control group, which suggests diminished responsiveness and confirms the findings of Bayliss and Heath.[6]

There was no evidence of any deterioration in GFR due to lithium. Although the GFR as assessed by endogenous creatinine clearance was perhaps low on average compared with generally accepted standards, it was not lower in the lithium group than in a group matched for age and sex taking other psychotropic drugs. Hestbech *et al*[3] reported that patients receiving long-term lithium treatment have a reduced GFR and interstitial nephropathy. Hansen and Amdisen,[7] who investigated 21 patients who had developed intoxication during long-term treatment with lithium (average duration of treatment 10 months to 7 years), reported that water loss due to impaired renal concentrating ability seemed to be a major predisposing factor for intoxication. In seven patients renal biopsy showed abnormalities suggesting a chronic nephropathy, possibly caused by lithium, which might be another predisposing factor. Hestbech and Amdisen reported a case of probable lithium-induced uraemia in a patient given regular lithium treatment for only three years; they also found that eight out of 110 patients treated with lithium for more than six months had signs of reduced renal function. Abnormal histological findings in the kidneys of lithium-treated patients were confirmed by Burrows *et al*,[8] who also reported an additional unique tubular lesion in patients taking lithium. Other workers[9 10] found that long-term lithium treatment damages the kidney, but some of the patients examined had had previous episodes of lithium intoxication and many had severe polyuria.

Our failure to find a reduced GFR in the lithium group could be due to error in measuring GFR from creatinine clearance, use of an inappropriate control group, or a real difference between our lithium-treated patients and those investigated by others. Abnormal glomerular function is difficult to detect with creatinine clearance because of errors in urine collection and the large variability in normal clearances, particularly with age. Nevertheless, whereas the urine collections may have been incomplete in the outpatients despite the precautions taken, this is most unlikely to have been the case in the inpatients because of the personal supervision. In any event none of these problems would explain our failure to find a difference between the lithium and control groups. Our controls were taking psychotropic drugs other than lithium and might themselves have had diminished renal function. The use of such a control group, however, can be justified since the treatment for recurrent affective disorders is not lithium or nothing but antidepressant drugs with or without anti-manic drugs given symptomatically for each episode of affective illness. It may, indeed, be argued that it was not appropriate to choose donor kidneys not used for transplantation as the control specimens for histological studies.

There was, however, a major difference between our lithium-treated patients and those investigated by others—namely, we used smaller and divided doses of lithium. In a study by Hestbech *et al*[3] five out of 14 patients had had previous episodes of lithium intoxication and the average 12-hour serum lithium concentration for the whole group was 0·94 ± SD 0·09 mmol/l (0·65 ± SD 0·06 mg/100 ml), which was much higher than the average concentration used by us (0·59 ± 0·17 mmol/l; 0·41 ± 0·12 mg/100 ml). Our method of management was also associated with a lower incidence of polyuria and hypothyroidism. Only 6 (5·7%) of our 106 patients had polyuria, whereas this occurs in over 30% of patients in other centres. Only 9 (8·5%) of our patients had hypothyroidism,[12] defined as a definite and persistent rise in thyrotrophic hormone, whereas this occurs in 15-33%[13-15] of patients in other centres. Our doses were adequate for prophylaxis, however, as there was no increase in the frequency of clinical relapse in patients with unipolar or bipolar disorders treated with long-term lithium until the 12-hour plasma lithium concentration fell below 0·4 mmol/l (0·3 mg/100 ml), when the yearly frequency of relapse increased from 10-15% of patients to over 50%.[16]

These findings support the suggestion that the lack of significant effects of lithium on renal function in our patients was due to our use of smaller but equally effective doses of lithium. Nevertheless, since it is common to continue lithium treatment for many years, if not indefinitely, and because the nephrotoxic effects of other drugs such as analgesics take decades to develop, longer observation will be necessary even at these smaller doses before lithium can be exonerated as an agent that might produce unwanted effects on the kidney.

We thank the nursing staff of the research unit and the technicians of the pathological laboratory at Hurst Royds Hospital, the technicians of the department of chemical pathology, University of Leeds, for invaluable help, and Dr R. M. Donald, High Royds Hospital, for permission to study his patients. This work was supported by a Medical Research Council programme grant to E.H.

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SHORT REPORTS

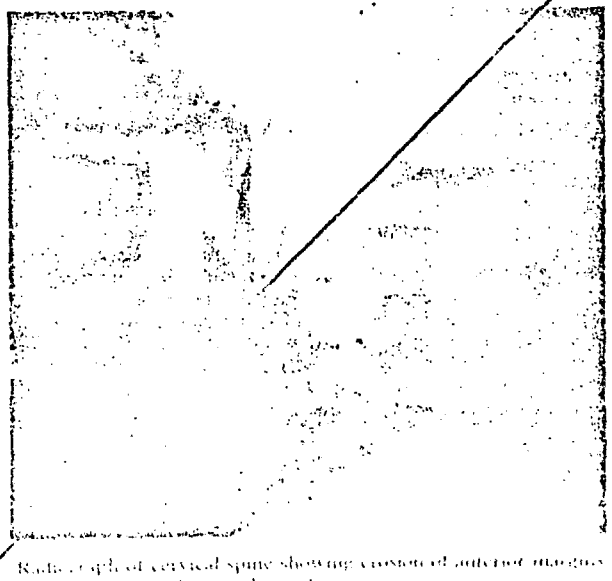
Pyogenic meningitis due to a vertebral abscess

Cervical vertebral abscess is a rare cause of meningitis. Diagnosis may be difficult as its symptoms and signs may be overshadowed by those of meningitis, as shown in the following case.

Case report

A 47-year-old man was admitted in September 1978 with a history of headache for two weeks, deteriorating vision for five days, and nausea and vomiting for two days. Three months earlier he had fallen in the snow, hurting his left shoulder, and since then he had had constant pain in the left shoulder, radiating to the left side of his neck and to the occipital region. He had suffered from night sweats and had lost 13 kg. His neck had been stiff for about two months. In June 1969 he had been treated for an extensive carcinoma of the pyriform fossa with radical cobalt radiation.

On examination he was obese, fully conscious and orientated, but aggressive and in pain. His temperature was 38·3 C; he had appreciable neck stiffness, a positive Kernig's sign, bilateral papilloedema, and small pupils. There were no focal neurological signs. A computerised axial tomographic scan was normal. Lumbar puncture showed a cloudy cerebrospinal fluid which contained 1·71 10^9 white cells/l (95% polymorphs and 5% lymphocytes); protein 1 g/l and glucose 0·5 mmol/l (9 mg/100 ml). A Gram stain showed no organisms and culture was negative. Radiographs of his cervical spine showed only minor degenerative changes.



Radiograph of cervical spine showing erosion of anterior margins of fourth and fifth cervical vertebrae

He was treated with analgesics and high doses of penicillin and sulphadiazine and dexamethasone. Although he improved symptomatically with the loss of his headache, he continued to have neck stiffness and he remained feverish after two weeks of chemotherapy. Radiographs of his cervical spine with tomography now showed erosion of the anterior margins of the fourth and fifth cervical vertebrae adjacent to the disc, together with narrowing of the disc space and soft tissue swelling at this level (see figure). A technetium scan showed a high diffuse uptake throughout the cervical spine.

He then developed weakness of the right arm and signs of cord compression at C4-5 and his general condition deteriorated. An exploration of the neck was performed through an anterior approach, and necrotic material was aspirated from the disc space between C4 and C5. Bilateral ventricular drains were inserted. Bacteriological examination of the aspirate showed numerous neutrophils, Gram-positive cocci, and Gram-negative rods. Culture of both aspirate and ventricular cerebrospinal fluid showed a heavy growth of β-haemolytic streptococci and *Bacteroides melaninogenicus*; both organisms were sensitive to penicillin. Fifty days after admission he died.

Necropsy showed evidence of a severe meningitis. The bodies of the fourth and fifth cervical vertebrae were collapsed and the centres were necrotic and infected. Pus communicated with the spinal canal through a hole in the posterior longitudinal spinal ligament which had been eroded at this level. Histological examination showed an acute purulent meningitis and the remains of an abscess within the fourth and fifth cervical vertebrae. There was no evidence of carcinoma affecting the cervical vertebrae.

Comment

The history of neck pain, night sweats, and weight loss, together with the presence of severe neck stiffness which was out of proportion to the other signs of meningitis, suggested the possibility of a cervical spine abscess. Normally a bone scan with technetium-99 is useful in diagnosing spinal osteomyelitis: in a series reported by Frederickson *et al*[1] a scan was positive in 12 out of 12 patients with spinal abscesses. But in our patient the diffuse isotope uptake in the cervical spine, due to the presence of meningitis, obscured the underlying abscess. Changes on radiographs of the spine occur late, and in this patient convincing evidence of an abscess was obtained only after tomography.

The organisms isolated from this patient's abscess and cerebrospinal fluid were unusual and were common flora of the mouth. He probably grew in an area of irradiation fibrosis in relationship to his previous treatment for carcinoma of the pyriform fossa. It is clearly important to aspirate and culture the pus. Failure of the patient's meningitis to respond to appropriate antibacterial treatment emphasises the importance of early surgical drainage when a spinal abscess is associated with meningitis.

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in digital vessel patency rates between 15°C and 21°C justify using this thermal stress.

In our patients plasma exchange significantly improved digital vessel patency rates at both 15°C and 21°C. Plasma exchange is known to be a potent method of defibrination.[15] Furthermore, plasma fibrinogen is a major determinant of whole blood viscosity at low shear rates. Thus the concept that narrowed digital vessels, initially impassable to viscous blood, are able to transmit blood rendered less viscous by plasma exchange appears attractive. Nevertheless, like Browse[16] we cannot explain why short-term reduction in plasma fibrinogen concentrations results in a long-term symptomatic improvement, and, in our patients, also quantitative evidence of improvement. This long-term improvement may be explained partly by changes which have been observed in the deformability of the red blood cells,[17] but the possible role of circulating immune complexes[7] still needs clarification and is the subject of continuing investigation.

We thank the Medical Research Council, Mecca Ltd, and ICI Ltd for their generosity in supporting this investigation, and the many members of the department without whose help and encouragement this work would not have been possible.

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(*Accepted 7 March 1979*)

Indomethacin increases plasma lithium

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British Medical Journal, 1979, 1, 1115-1116

Summary and conclusions

The effects of indomethacin on plasma lithium concentrations and renal lithium clearance were investigated in three psychiatric patients and four normal volunteers. After steady-state plasma lithium concentrations had been reached, the subjects received indomethacin placebo for three to seven days, indomethacin (50 mg thrice daily) for seven days, and placebo again for three to seven days. Indomethacin increased plasma lithium concentrations by 59% in the psychiatric patients and 30% in the volunteers. Renal lithium clearance was reduced by indomethacin by 31% in the group as a whole, and prostaglandin synthesis, determined by measuring the major metabolite of PGE_2 with mass spectrometry, was reduced by 55%.

These results show that indomethacin reduces renal lithium clearance to an extent which may be clinically important. They also suggest that the renal clearance may be affected by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

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Introduction

Lithium is being given to increasing numbers of patients for the treatment of manic depressive and other psychiatric illnesses.[1] This treatment is not without hazards, and fatal lithium intoxication has been reported.[2] We describe here a drug interaction between lithium and indomethacin which could make the simultaneous administration of these drugs hazardous. We also provide evidence for a novel prostaglandin-mediated excretory mechanism of lithium.

Patients and methods

The study was carried out in three psychiatric patients in the manic phase of their disease and in four normal volunteers. The study was started when steady-state lithium concentrations had been reached, which usually required over three weeks of constant lithium intake in the patients and 10 to 14 days in the normal volunteers. Steady state was defined as plasma lithium concentrations on three consecutive days within 0·1 mmol/l (mEq/l) of each other. The patients and volunteers were kept on free diet throughout the study and received no other drugs.

The study consisted of three periods in which lithium intake was constant. In the first period an indomethacin placebo was given for three to seven days, in the second indomethacin was given in a dose of 50 mg three times a day for seven days, and in the third placebo was given for three to seven days. Throughout the study we determined plasma lithium concentrations daily 12 hours after the last dose and lithium and creatinine in daily 24-hour urine samples. On the last day of each period 7α-hydroxy-5, 11-diketotetranorprostan-1, 16-dioic acid (PGE-M) was determined by gas chromatography-mass spectrometry to assess the rate of prostaglandin synthesis. On each patient underwent psychiatric evaluation on the Brief psychiatric rating scale, sad-glad scale, and Minnesota personality inventory.

Results

Indomethacin increased plasma lithium concentrations in all the psychiatric patients and volunteers. The average increase in the plasma lithium concentration (average of the last two days on indomethacin) over values in the first placebo period was 50% in the psychiatric patients and 30% in the normal volunteers (fig 1). In all subjects studied plasma lithium values increased by 42±8% (mean ± SE; $P<0.01$), and fell in the second placebo period to 116±5% ($P<0.01$) of control (=100%). A representative study in one of the psychiatric patients is shown in fig 2. Indomethacin increased the plasma lithium concentration from 0·95 to 1·5 mmol/l within five days. The patient was switched back to placebo at that point to avoid toxicity and the plasma concentrations promptly declined. Indomethacin also reduced urinary lithium excretion.

Renal lithium clearance was suppressed by indomethacin in all the subjects by an average of 31±3% (fig 3) and tended to return to pre-indomethacin values in the second placebo period.

The values for PGE-M in the three study periods were 8·1±3, 3·7±0·5 ($P<0.01$), and 10·8±3 µg/g creatinine ($P<0.01$).

None of the psychiatric tests showed that indomethacin had any harmful effect.

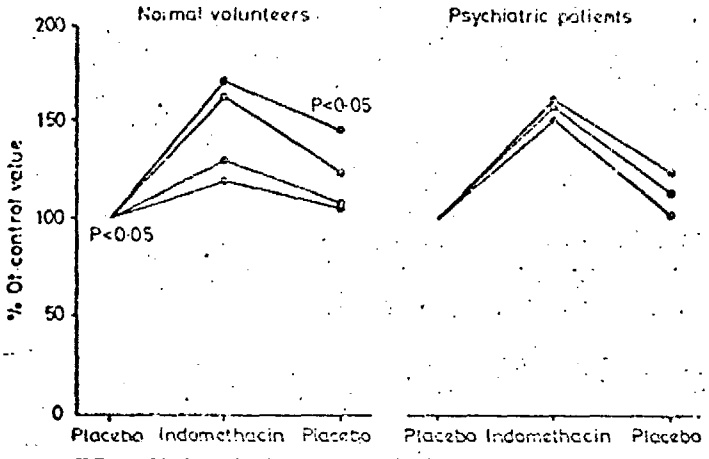

FIG 1—Effect of indomethacin on plasma lithium concentrations in normal volunteers and psychiatric patients.

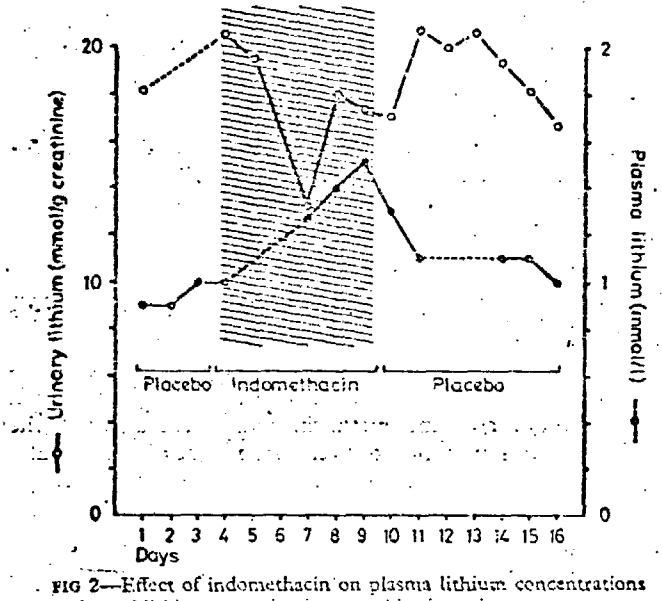

FIG 2—Effect of indomethacin on plasma lithium concentrations and renal lithium excretion in a psychiatric patient.

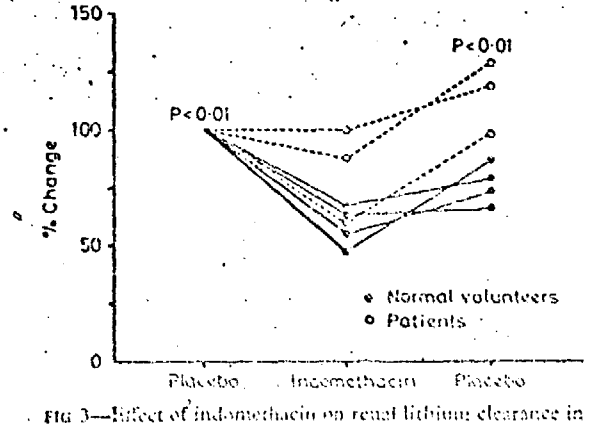

FIG 3—Effect of indomethacin on renal lithium clearance in patients and normal volunteers.

Discussion

Our results show that indomethacin causes a clinically relevant drug interaction with lithium. The increase in plasma lithium concentration was enough to lead to toxicity, and seems to have been caused by a reduction in renal clearance of lithium, since the size of the increase in the plasma concentration corresponded reasonably well to the size of the decrease in renal clearance. The cause of the reduction in renal lithium clearance by indomethacin is obscure. Indomethacin has no effect on glomerular filtration rate in man.[2]

Indomethacin regularly causes sodium retention in man, however,[1] thus suggesting that enhanced sodium and lithium reabsorption might be caused by a similar mechanism. Recent studies on the site of action of prostaglandin synthesis inhibitors such as indomethacin on sodium transport have shown that these inhibitors cause an enhanced medullary sodium concentration.[3] Furthermore, prostaglandin E_2 injected into the distal tubule decreases net distal tubular sodium efflux,[4] and in the isolated cortical collecting tubule peritubular prostaglandin E_2 inhibits sodium transport.[5] All these findings suggest that prostaglandins have an effect on distal tubular transport. Nevertheless, lithium is thought to be reabsorbed only in the proximal tubule[6] because diuretics that decrease distal sodium reabsorption do not enhance lithium excretion.[7]

Our results show that indomethacin reduces renal clearance of lithium to an extent that may be clinically important. They also suggest that the renal clearance of lithium may be influenced substantially by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

This work was presented in part at the Annual Meeting of the American Federation for Clinical Research, San Francisco, May 1978, and was supported by PHS-NIH grants HL 14192, GM 15431, 5-MO 1-55-000-95 and the Robert Bosch Foundation, Stuttgart. We are grateful to Ms M Cameron for valuable laboratory help.

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Annex 5

ADVERSE INTERACTION BETWEEN LITHIUM AND TETRACYCLINE: Despite its extensive usage, there have been infrequent instances of adverse interactions between lithium and other medicines. To date those that have been reported include interaction with diuretics, antibiotics, and neuroleptics. To this catalogue must be added a potentially serious interaction between lithium and tetracycline. (1). This occurred in a 30-year-old bipolar woman who, for 3 years, had been stabilized by 1600 mg lithium a day producing a serum concentration ranging from 0.5 to 0.84 mEq/l. After developing a vaginal discharge, she was started on tetracycline 250 mg long-acting capsules (Tetrabid - Organon) two as the first dose and one three times a day thereafter. Two days after the start of tetracycline therapy, a routine serum lithium disclosed a dramatic rise to 1.7 mEq/l. Four days after initiation of tetracycline therapy, her speech was slurred, she was slightly drowsy and she had excessive thirst accompanied by a fine tremor of both hands. At that time, her serum lithium was 2.74 mEq/l. Lithium and tetracycline were discontinued. Three and 5 days later her serum lithium concentrations were 1.89 and 0.28/mEq/l respectively. This rapid decline in serum lithium was accompanied by a prompt abatement of all signs of toxicity.

EDITOR'S COMMENT: This is the second published report of an adverse interaction between lithium and an antibiotic; the first was published in the April 1978 issue of this Newsletter. Both of these case reports illustrate the danger of co-prescribing lithium with a drug that may sometimes have a nephrotoxic effect (2). Tetracycline has been known to produce anorexia, nausea, vomiting, sodium diuresis, and polyuria in individuals who already have renal insufficiency. (3). There are two important lessons taught by these cases. These are: (1) a physician should always be on guard when lithium is co-administered with any drug that may affect renal function, even if the drug is an antibiotic; and (2) whenever lithium is co-prescribed with a drug known to affect renal function, serum lithium should be checked within a few days after the combined therapy was started, since the early stages of lithium intoxication are often symptomless.

In hyperphosphataemic patients aluminium hydroxide therapy must be continued to bind phosphate in the gut and so prevent an increase in plasma phosphorus and consequent soft-tissue calcification.

CONCLUSION - Alfacalcidol and calcitriol have the advantage that the hypercalcaemia they may cause disappears faster when the drug is stopped than with calciferol, cholecalciferol and dihydrotachysterol. This makes alfacalcidol and calcitriol easier to use, particularly in the management of hyperparathyroidism in chronic renal failure. The best choice of drug for any purpose, and the best way of using it, remain unclear.

Basic NHS Costs of 4 weeks' treatment

Alfacalcidol (One-Alpha)	1 mcg daily,	£ 7.00
Strong calciferol tablets BP	2.5 mg daily,	45p
Dihydrotachysterol (AT10)	1 ml daily,	£12.92
(Tachyrol)	0.2 mg daily,	£ 2.58

*Cholecalciferol is not available commercially. Capsules containing 0.25 mg and 1 mg are made by the pharmacy at University College Hospital, Gower Street, London WC1E 6AU. They can be supplied in multiples of 1000, but are not always immediately available.

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RENAL TOXICITY OF LITHIUM

Lithium has been used increasingly for the prevention of episodes of affective disorder, both manic and depressive. It has also been advocated in the management of other psychiatric conditions such as schizophrenia, alcoholism and personality disorder. However, it has a low therapeutic index. In particular, it induces polyuria and polydipsia[1] which may be transient, recurrent or persistent. They are symptoms of nephrogenic diabetes insipidus,[2,3] and are particularly prevalent in patients receiving additional psychotropic drugs.[4] Between 5 and 30% of patients taking lithium suffer from polyuria, depending on dosage, dosage interval and total amount of lithium ingested; it may occur even after short-term treatment. The mechanism is that lithium inhibits the effect of antidiuretic hormone (ADH) on the kidney and so inhibits the ability of the kidney to concentrate urine.

Renal biopsy findings - Lithium toxicity and the nephrogenic diabetes insipidus which it causes are usually regarded as reversible. However, biopsies from patients with these complications show a high incidence of focal glomerular sclerosis, tubular atrophy and/or interstitial fibrosis.[5-8] The impairment of concentrating ability correlates with the histological changes, suggesting that it is a sign of permanent damage. Polyuria increases the risk of dehydration and lithium intoxication, but its relationship to the histological changes is unclear. Also, the changes progress slowly and the risk of death from renal failure is believed to be small.[6,9] In these reports patients had symptoms of toxicity or abnormal renal

function tests before their biopsies. By contrast, biopsies have been carried out on a pair of monozygotic twins maintained on lithium, in one of whom toxic effects had developed. That twin's biopsy showed interstitial fibrosis and his creatinine clearance remained impaired for nine months after lithium was discontinued. The twin who had never shown lithium intoxication had almost normal renal function but his biopsy also showed interstitial fibrosis, suggesting that renal damage can occur without symptoms.[10]

Biopsies have also shown tubular changes, including a unique lesion in the distal tubules and collecting ducts in patients with normal serum creatinine and urea and normal urine.[11] These changes were noted in two patients who had taken lithium for only four and five months, but were more advanced in those who had taken lithium for longer.

Prevention - These findings are worrying. Until more is known about the incidence and long-term effects of these pathological changes lithium should only be used to control recurrent mania, mania alternating with depression and clear-cut recurrent depression; its use in other conditions should be avoided unless undoubted therapeutic benefit can be demonstrated on a trial basis. The choice in patients with recurrent affective disorders is not between lithium and no drug, but between lithium and other psychotropic drugs such as tricyclic antidepressives and antipsychotic agents, all of which have their own problems of long-term toxicity. Nevertheless, a patient should only be maintained on lithium if benefit persists and if attempts to withdraw lithium (at intervals of, say, 3-5 years) are associated with a recrudescence of attacks. The serum lithium concentrations should be kept as low as possible in the therapeutic range.

CONCLUSIONS AND RECOMMENDATIONS - Lithium should not be prescribed unless treatment will be properly monitored. Before starting treatment with lithium, a urine analysis and urine concentration test should be performed and the serum creatinine measured. These should be repeated at intervals of not more than a year. Lithium should be given in twice daily dosage, so that its concentration in the glomerular filtrate will be less than with the same dose given once daily.

Patients should be instructed to report promptly any polyuria or polydipsia, and also attacks of diarrhoea and vomiting (which may predispose to lithium toxicity by depleting body sodium). They should also be advised not to make major changes in their diet without medical advice. Serum lithium concentrations must be measured regularly in all cases. It seems desirable to provide printed information cards for patients on lithium.

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ovarian cyst formation. The first was performed in Northern Ireland when she was 16 years of age. She had had chronic pelvic pain since that time and a pelvic mass had re-formed on three occasions. The most recent "cyst" proved to be an inflammatory mass consisting of chronically infected omentum fixed to her remaining right tube and ovary. The omental mass was removed and the tube and ovary restored to an apparently normal condition. Within five days of operation a tender mass had re-formed. Laparoscopy on the eighth postoperative day confirmed that once more the omentum was matted around the tube and ovary. The tissues were all separated and dye studies showed that the tube was still patent. The patient was discharged the following day. She was seen recently, six months after discharge from hospital. She had been free of pain for the first time in 10 years and vaginal examination showed no obvious pathology. Marriage is contemplated and were she to conceive one would feel that a further advantage had been obtained.

It must be stressed that in each case postoperative problems were present, indicating persistent disease. Each time the laparoscopic procedure has relieved the patient of unpleasant symptoms; there have been no obvious repercussions and all remain symptom-free to the present time. The procedure requires great care and should, I feel, be practised only by surgeons with a wide experience of laparoscopic operating.

E G SIMONS

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Chasing the cause of Crohn's disease

SIR,—Your leading article (9 April, p 929) drew attention to two papers, one of which suggests that a common breakfast cereal, corn flakes,[1] and the other that food additives[2] may play a part in the aetiology of Crohn's disease.

We are presently following up two cases of Crohn's disease in children, one of which is undoubtedly aggravated, if not caused, by foods and the other by additives.

Case 1—This girl was first seen at the age of 9 as she had developed peritonitis due to multiple perforations associated with Crohn's disease of the small bowel. The lesion was removed surgically. The histological appearances were characteristic of Crohn's disease, many multinucleated giant cells being present.

After the operation she was asked to avoid cow's milk and dairy products and peanut butter—the latter because its ingestion was associated with diarrhoea. Four months later, on no medication, she was so well that she was allowed to take milk. Within a month she had to be readmitted to hospital as her diarrhoea, fever, and spells of abdominal pain had returned. On this occasion she was taken off all oral fluids and maintained on hyperalimentation. Her symptoms settled, and when all evidence of active disease had subsided she was once more allowed foods, but on this occasion she was offered the foods one at a time and any food which precipitated spells of abdominal pain or diarrhoea was excluded. On her restricted diet she remained symptom-free and gained weight. To remain well she has to avoid all milk and dairy products, ham, and bacon, as well as blueberries and cakes containing poppy seed. This child has at no time had steroids.

Case 2—This is a boy who first presented with diarrhoea associated with obvious blood loss when he was given cows' milk at the age of 6 months. He reacted similarly to many other foods, soya included. Drugs, even aspirin, had to be avoided for they too caused a return of his bloody diarrhoea. For this reason he had to be brought up on a very restricted diet but remained relatively well until he was 13 years old, when he developed spells of abdominal pain and vomiting associated with fever and weight loss. Radiological studies indicated that he had linear ulcerations in the ascending colon, caecum, and distal 14 cm of the ileum, the last also having a cobblestone appearance. The sigmoid colon was normal. All oral foods and fluids were withheld and he was maintained on hyperalimentation alone. He received no steroid therapy. On this regimen his symptoms and fever settled and there was radiological evidence of recovery. When he was once more offered ordinary foods his symptoms gradually returned. He was therefore started on oral prednisone, but this was followed by an acute exacerbation of his pain and bloody diarrhoea and by radiological evidence of deterioration. He was therefore put back on hyperalimentation alone, and again his symptoms subsided completely. There was little doubt in our minds that "something" (in addition to foods) in the oral steroids (several preparations were tried), either lactose, starch, sugar, paraffin oil, or tartrazine, present in some of the preparations, aggravated his disease, for within 15-20 min of taking the preparation he would complain of an accentuation of his pain. As most foods, some more and some less, precipitated spells of abdominal pain and diarrhoea and as "something" in the oral steroid preparations also caused a return of his disease we decided to maintain him on long-acting corticotrophin (ACTH) and the foods that he best tolerated. On this regimen he is once more growing and developing normally and is symptom-free.

Two features in the above cases suggest that diet is related to the disease. Firstly, in each case the exclusion of all foods and fluids by mouth, with reliance on hyperalimentation alone, led to recovery; secondly, the reintroduction of a few selected foods in case 1, and of many more foods and additives in case 2, caused a relapse.

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[2] Martini, G A, and Brandes, J W, *Klinische Wochenschrift*, 1976, 54, 367.

Absorption of lithium from controlled-release preparations

SIR,—Dr R P Hullin (21 May, p 1349) inadvertently gives the impression that *all* lithium carbonate tablets *BP* will necessarily have the same bioavailability; this is not so.

The disintegration test specified in the *BP* 1973 is not a measure of bioavailability; it is quite possible to manufacture tablets which comply with the specifications of the *BP* 1973, including disintegration, but produce lithium blood levels of a completely different pattern from those produced by the two products on the market. This is because the bioavailability of lithium is controlled by many factors in tablet formulation and manufacture which are not mentioned in the *BP* monograph and which are not controlled by the *BP* specification.

The bioavailability pattern of Camcolit 400 has been shown by Dr Hullin to be similar to that of Priadel and we agree with him that these two products are interchangeable; there seems little doubt that the Department of Health and Social Security will require any future products they licence to match the same pattern.[1 2] However, there is, theoretically, nothing to stop a hospital pharmacy producing tablets to the existing *BP* specification which could have a completely different pattern of bioavailability.

M R SCOTT

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[1] Stewart, A G, *Pharmaceutical Journal*, 1977, 218, 254.
[2] Florence, A T, *Pharmaceutical Journal*, 1977, 218, 255.

Efficacy of measles vaccination

SIR,—The letter from Drs M D Coulter and B M Jones (21 May, p 1347) stirred some distant memories.[1 2] It also disturbed me a little that unvarnished "truth" has become a rare commodity in preventive medicine.

If a susceptible infant is actively immunised against measles there is, approximately, an 85% chance that he will escape measles infection in the next few years. Well over 90% of the herd will need to be immune if the virus is to be kept from gaining a toe-hold. Such an environment may be created in an isolated atoll in the Pacific. You could not hope for it in the mobile population of England.

The vaccine-produced immunity does wane as time goes by, while the potency of the vaccine is adversely affected by unfavourable storage conditions and by plunging the needle through skin to which is still clinging a viricidal cleansing agent.

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Glucose-6-phosphate dehydrogenase deficiency and duodenal ulcer

SIR,—Since 1970 we have been studying the distribution of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency in Sardinian patients of the Ospedali Riuniti of Sassari. It is well known that the prevalence of the deficiency in Sardinia is very high[1] and is almost exclusively of the Mediterranean type—for example, it is found in about 8% of our patients, who come to us from the north-western part of the island.[2]

In the past 18 months we have been comparing the prevalence of G-6-PD deficiencies in 175 male patients suffering from duodenal ulcer, confirmed surgically, with that in an equal number of patients suffering from diseases other than duodenal ulcer. The two groups were matched for sex, age, and place of origin. The results are reported in the table, from which it will be seen that the prevalence of G-6-PD deficiency in patients with duodenal ulcer (14·85%) is double that in the controls (7·42%); this difference is statistically significant.

G-6-PD deficiency in male patients with duodenal ulcer and in controls

Group	No deficient	No non-deficient	Total
Duodenal ulcer ..	26	149	175
Controls	13	162	175
Total ..	39	311	350

χ^2 (with Yates's correction) = 4·15 ($P < 0·05$).

PROGRESS REPORT

Date Application received: 20-2-75

Product Number: PL/0322/0012

Application for Product Licence or Clinical Trial Certificate	Date submitted: Sub-Committees: MCT	BIO	CPS/ Herbals	Main Committee	Proposed Recommendation	Date of Appeal	Final Recommendation	Product Licence or Clinical Trial Certificate Number	Date of Issue Product Licence or Clinical Trial Certificate
PL					Application Withdrawn				
				27.1.77	T Def.				
				27.1.77	Agreed	-	Agreed	PL/322/005	