DIAZEPAM RECTAL TUBES

EXPERT REPORT ON CLINICAL DOCUMENTATION

CP Pharmaceuticals Ltd.

Clinical Expert Report

1   Problem Statement

Intravenous diazepam is an essential emergency medication and the drug of choice for the initial treatment of prolonged seizures or epileptic convulsions (Schmidt et al 1993). However, use of the intravenous route is restricted by the necessary presence of physicians or suitably skilled nursing staff. Additional difficulties in these indications arise from the movements of patients with these conditions. Venepuncture may become difficult or impossible and might even endanger the patient and doctor.

Other pharmaceutical formulations such as tablets, suppositories or intramuscular injections have been evaluated with regard to their pharmacokinetic properties and potential acute anticonvulsant effects. However, it was found that the delay in reaching adequate plasma levels was too great to provide a reasonable alternative route of administration in an emergency (Moolenaar et al 1980).

The product discussed in this report, Diazepam Rectal Tube, is a device to instill a specially formulated solution rectally; it has been developed to promote the rapid rectal absorption of the drug. The rectal tube is easy to handle and can be administered by nursing staff not trained in the intravenous technique and by people with no medical training (eg. parents, relatives of epileptic patients). The rectal tube is particularly useful in the treatment of children, providing a valuable painless alternative to intravenous injection.

Thus, Diazepam Rectal Tubes can be used when the anticonvulsant, sedative and muscle relaxant properties of diazepam are required. The product may be used in severe or disabling anxiety and agitation; epileptic and febrile convulsions; tetanus; as a sedative in minor surgical and dental procedures, or other circumstances in which a rapid effect is required but where intravenous injection is impracticable or undesirable. Diazepam Rectal Tubes may be of particular value for the immediate treatment of convulsions in children.

To facilitate dose adjustment, two strengths are available: tubes with 5 mg diazepam and tubes with 10 mg diazepam.

2   Clinical pharmacology

2.1   Pharmacodynamics

Diazepam is a psychotropic substance from the class of 1,4-benzodiazepines with marked properties of suppression of tension, agitation and anxiety as well as sedative and hypnotic effects. In addition, diazepam demonstrates muscle relaxant and anticonvulsive properties.

Diazepam can be used in the short-term treatment of anxiety and tension states, as a sedative and premedicant, in the control of muscle spasm and in the management of alcohol withdrawal symptoms.

Diazepam binds to specific receptors in the central nervous system and particular peripheral organs. The benzodiazepine receptors in the CNS have a close functional connection with receptors of the GABA-ergic transmitter system. After binding to the benzodiazepine receptor, diazepam augments the inhibitory effect of GABA-ergic transmission.

2.2 Pharmacokinetic properties

After rectal administration of the solution, diazepam is absorbed rapidly and almost completely from the rectum.

The onset of the therapeutic effect occurs within a few minutes of rectal administration. The rapidity of the rise in the serum level following rectal administration corresponds approximately to that following an intravenous dose but peak plasma concentrations are lower after rectal tubes than after intravenous administration. In adults maximal plasma concentrations following the administration of 10 mg diazepam in rectal solution are reached after about 10 -30 minutes (ca. 150 - 400 ng/ml). Occasionally adsorption to the faeces in the rectum can affect absorption (Magnussen et al 1979).

Diazepam is extensively protein bound (95-99%). The volume of distribution is between 0.95 and 2 l/kg depending on age. Diazepam is lipophilic and rapidly enters the cerebrospinal fluid. Diazepam and its main metabolite, N-desmethyldiazepam, cross the placenta and are secreted in breast milk.

Diazepam is metabolised predominantly in the liver. Its metabolites, N-desmethyldiazepam (nordiazepam), temazepam and oxazepam, which appear in the urine as glucuronides, are also pharmacologically active substances. Only 20% of the metabolites are detected in the urine in the first 72 hours.

Diazepam has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1-2 days. For the active metabolites N-desmethyldiazepam, temazepam and oxazepam, the half-lives are 30-100 hours, 10-20 hours and 5-15 hours respectively. Excretion is mainly renal and also partly biliary; it is dependent on age as well as hepatic and renal function.

Metabolism and elimination in the neonate are markedly slower than in children and adults. In the elderly, elimination is prolonged by a factor of 2 to 4. In patients with impaired renal function, elimination is also prolonged. In patients with hepatic disorders (liver cirrhosis, hepatitis), elimination is prolonged by a factor of 2.

2.3 Justification for the dosage

Time to peak and maximum plasma concentrations vary considerably following rectal administration of diazepam and the relationship between blood levels and activity is not well established. However, it is important, particularly in the control of convulsions, to provide for an adequate initial dose of diazepam so that plasma levels are reached quickly that are sufficient for a therapeutic effect but not so high as to cause adverse events such as respiratory depression. Should the desired effect not be achieved, it is appropriate to make recommendations on the timing and quantity of repeat dosing.

Plasma levels between 300 and 400 ng/ml have been suggested for an adequate anxiolytic response (Gilman et al 1990). A beneficial response in tetanus (with muscle spasms and rigidity) was associated with a minimum serum diazepam concentration of 500 ng/ml (Dasta et al 1981). Levels above 600 ng/ml (Browne and Penry 1973; Gilman et al 1990) or even 700 ng/ml (Leal and Troupin 1977) may be necessary for control of seizures. Some authors suggest that lower plasma levels, between 150 and 250 ng/ml, are effective Agurell et al 1975; Remy et al 1992). However, levels that fall below 150 to 200 ng/ml have been associated with break-through seizures (Agurell et al 1975).

Table 1

Summary table for studies of the anticonvulsant effect of rectal diazepam involving measurement of serum concentration

Ref	Subjects & Dose of Diazepam	Time to peak serum conc	Peak serum conc ng/ml	Time to reach anticonvulsant level
Agurell, 1975	16 children 0.12-0.45mg/kg	usual 10 min (up to 30)	145-1135	<10 min in all
Knudsen, 1977	20 infants 0.7mg/kg	10 min	1449	4 ± 1 min
Dulac, 1978	19 infants/children; 0.25-0.5mg/kg	6min	845	2min
Moolenaar, 1980	9 healthy adults 10mg	17min	369	
Viukari, 1981	6 elderly (mean age 76) 10mg	27.5min	164	
Krag, 1982	4 adults 10-20mg (0.13-0.26mg/kg) 4 adults 30-53mg (0.41-0.7mg/kg)	10 ->60 min 30 - 60min	138-426 484-756	not reached in 3/4 7 - 10

This knowledge, together with clinical experience and the results of bioavailability studies, has led to the recommendation that a dose of 0.5 mg/kg in children and adults is necessary to achieve a 'therapeutic' level of diazepam for an anticonvulsant effect.

For an average adult (60 kg), a dose of 30 mg has been shown to be necessary to provide anticonvulsant blood levels (Krag et al 1982; Remy et al 1992). Administration of only 10mg, ie a single Diazepam Rectal Tube is probably inadequate (Moolenaar et al 1980; Dhillon et al 1982; Magnussen et al 1979).

Some authors recommend a dose of 0.5 to 1.0 mg/kg (Schmidt, 1989) for anticonvulsant emergency treatment. However, it should be noted that most of the serious adverse reactions have been observed at dosages between 0.5 and 1.0 mg/kg (Hoppu et al 1981; Knudsen 1979; Kruse 1983). In the elderly and debilitated patients, the dose should be reduced because the elimination half life is prolonged and there is a greater risk of

postural hypotension, unsteadiness and falls. Dose reductions may also be necessary in patients with liver or kidney dysfunction.

In children, it is appropriate to determine the dose by patient weight rather than age; a dose of 0.5 mg/kg has been recommended to provide anticonvulsant plasma levels without inducing side effects (Knudsen, 1977; Albano 1989; Dulac 1978; Hoppu et al 1981; Franzoni 1983). One 5 mg tube should provide a reasonable dose for infants weighing 10 - 14 kg, (requirement 5 - 7 mg). Children weighing over 15 kg, (requirement > 7.5 mg) may reasonably be given one 10 mg tube. As the minimum dosage form available is 5 mg, Rectal Tubes cannot be recommended for children under 10 kg body weight.

Regarding other indications, Lundgren (1985) recommended 0.5 mg/kg initially for adult outpatient sedation, followed by an additional 10 mg if the response was inadequate after 15 minutes. The same author reported (1986 and 1988) that a preset dose of 10 mg diazepam was inadequate for outpatient sedation whereas 0.5 - 0.6 mg/kg given rectally was as effective as 0.1 - 0.4 mg IV. Lundgren (1978) found that 10 mg in children weighing 15 - 25 kg (0.4 - 0.6 mg/kg) provided adequate sedation for dental procedures. In adults, 0.5 mg/kg provided adequate sedation for oral surgery (Lundgren et al 1984). Mattila (1981) reported that a dose of 0.4 - 0.5 mg/kg was needed to provide an adequate serum concentration for preoperative sedation in children within 5 - 6 minutes. Hassall (1984) used a mean dose of 0.5 mg/kg in children undergoing colonoscopy.

In children, peak plasma concentrations appear to be reached in about 10 minutes (range quoted 4 - 20, depending on the dose), with anticonvulsant levels being reached in 2 - 10 minutes (see Table 1). In adults, time to peak concentration is usually longer, probably 20 - 30 minutes (range quoted 10 - 60). In the elderly it was almost 30 minutes (Viukari 1981). Anticonvulsant levels are reached in approximately 10 minutes in adults (range quoted 7 - <15). Thus, if the clinical response is inadequate after 10 minutes, it is reasonable to recommend that the dose should be repeated in children; adults should be given one further 10 mg tube, not a repeat of the whole dose. In the case of prolonged seizures or epileptic convulsions unresponsive to diazepam, alternative treatment should be considered.

Thus, it is concluded that for all indications, the dosage recommendations should be as follows:

Children: 0.5 mg/kg (Under 10kg: not recommended . 10-15 kg: one 5 mg tube. Over 15 kg: one 10 mg tube).
Adults: 0.5 mg/kg (two to three 10 mg tubes).

If no effect is seen after 10 minutes, the dose can be repeated in children or an additional 10 mg tube given to adults. If convulsions are still not controlled other anticonvulsive measures should be instituted. The dose can be repeated every 12 hours.

Elderly and debilitated patients should be given not more than one half the usual adult dose. Dosage reduction may also be required in patients with liver or kidney dysfunction.

2.4 Bioavailability of the product

The bioavailability of Diazepam Rectal Tube has been evaluated in comparison with Diazepam Desitin Injection and with Stesolid Rectal Tube 10 mg (Dumex BV, The Netherlands), (Hefting et al 1992). In this study 18 healthy subjects received 10 mg

diazepam in a triple cross-over design with 21 days wash out between treatments. Blood samples were drawn over 216 hours; plasma was analysed for diazepam, N-desmethyldiazepam, temazepam and oxazepam using an HPLC-UV method. The results are given in Table 2 and presented graphically in Figure 1.

Table 2   **Pharmacokinetic parameters of Diazepam after rectal administration compared with IV administration**

| Parameter | Treat-ment | \multicolumn{3}{c}{Diazepam} | | | \multicolumn{3}{c}{N-Desmethyldiazepam} | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | n | mean | confidence intervals and point estimates of ratio of A to reference product (%) | | n | mean | confidence intervals and point estimates of ratio of A to reference product (%) | |
| C_{max} ($\mu g.L^{-1}$) | A | 18 | 225 | | | 18 | 34.4 | | |
| | B | 18 | 239 | 85-104 | 94 | 18 | 33.8 | 95-109 | 102 |
| | C | 18 | 733 | 27-34 | 31 | 18 | 38.0 | 83-99 | 90 |
| t_{max} (h) | A | 18 | 0.500 | | | 18 | 60 | | |
| | B | 18 | 0.417 | | | 18 | 72 | | |
| | C | 18 | 0.167 | | | 18 | 48 | | |
| $AUC_{0-\infty}$ ($\mu g.L^{-1}.h$) | A | 18 | 5144 | · | | 17 | 5790* | | |
| | B | 18 | 5227 | 93-104 | 98 | 17 | 5848* | 92-107 | 99 |
| | C | 18 | 6057 | 79-91 | 85 | 17 | 5972* | 88-106 | 97 |
| $t½$ (h) | A | 18 | 41.8 | | | 17 | 83.4 | | |
| | B | 18 | 40.2 | | | 17 | 84.9 | | |
| | C | 18 | 42.1 | | | 17 | 66.6 | | |

Treatment A: Diazepam Rectal Tube 10 mg; Treatment B: Stesolid Rectal Tube 10 mg; Treatment C: Diazepam Desitin Injection 0 mg.

* based on least-squares means from four-factor ANOVA

Maximum plasma concentrations were 733 ng/ml (range 393-1073 ng/ml) following IV administration and 225 ng/ml (range 138-319 ng/ml) following administration of Diazepam Rectal Tube. These maxima were reached after 10 minutes (range 10-30 minutes) by the IV route and after 30 minutes (range 10-50 minutes) by rectal administration. With regard to the main metabolite, N-desmethyldiazepam, maximal plasma concentrations were reached after 48 hours (range 16-168 hours) following IV administration and after 60 hours (range 16-168 hours) by rectal administration. The plasma concentrations of temazepam and oxazepam were too low to calculate pharmacokinetic parameters.

The extent of bioavailability of diazepam from the Diazepam Rectal Tube compared with IV diazepam amounts to 85% (95% confidence intervals: 79-91%). If the results for the metabolite, N-desmethyldiazepam, are taken into consideration as well, it can be concluded that Diazepam Rectal Tube is almost bioequivalent to IV administration of diazepam with respect to the extent of availability. With regard to the indication - acute treatment in certain emergencies - the rate of absorption is more important than
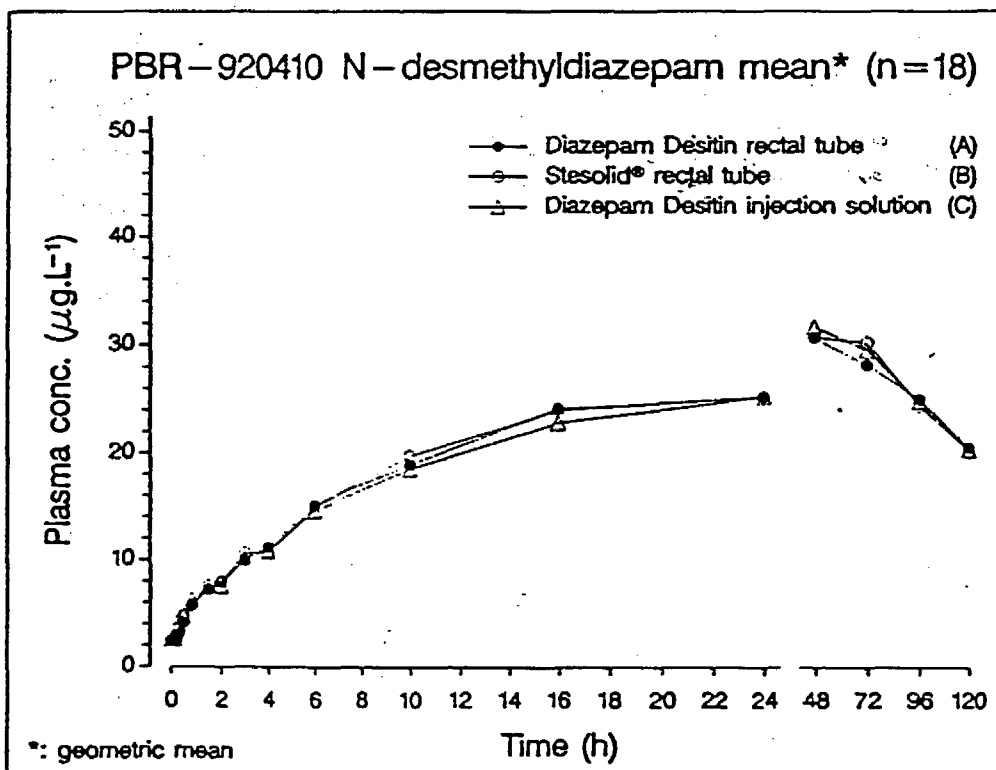
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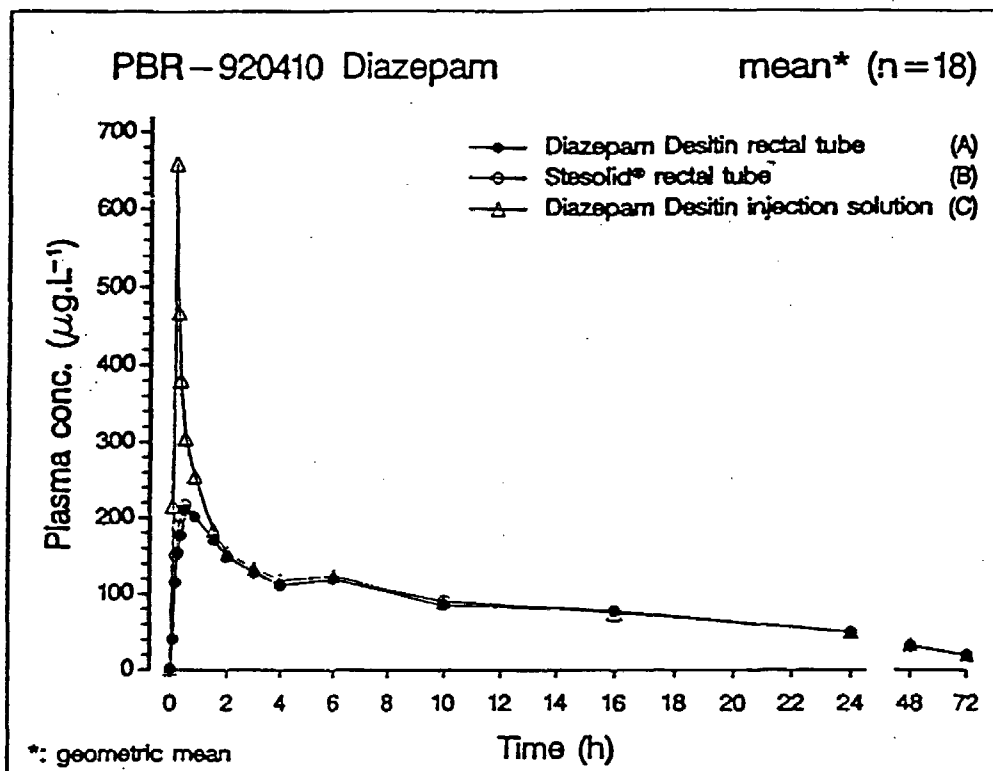
b.

Figure 1. Geometric mean plasma concentration profiles of diazepam (a) and N-desmethyl-
diazepam (b) after single dose administration of 10 mg of diazepam to 18 subjects

A = Diazepam Desitin rectal tube (DDrt-10 mg)

B = Stesolid® rectal tube

C = Diazepam Desitin injection solution (DDI-10 mg)

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bioavailability. The rate of absorption is slightly slower than that following IV administration, the peak occurring about 20 minutes later on average. However, this is fast when compared with absorption after administration by the IM or oral routes or rectal administration of suppositories.

This study also compared the pharmacokinetic parameters of Diazepam Rectal Tube with Stesolid Rectal Tube (Dumex). These two products have identical formulations but are manufactured by different companies. As can be seen from the results in Table 2, the 90% confidence intervals of the ratio of treatment A/B of C_{max} and AUC_{0-} were confined within the 80-125% limits for bioequivalence for diazepam and N-desmethyldiazepam. Therefore it is concluded that the test preparation (Diazepam Rectal Tube) and the reference preparation (Stesolid rectal tube) are bioequivalent.

Further support for the bioavailability of diazepam from a rectal solution (Stesolid Rectal Tube) compared with IV injection was provided by an earlier bioavailability study in nine healthy volunteers, (Moolenaar et al 1989). Each subject received 10 mg diazepam either rectally or IV in a cross-over design. Blood samples were drawn over 24 hours.

The ratio of the mean values and the respective standard deviations (rectal/IV) were:

C_{max}	0.54 (0.15)
AUC_{0-24}	0.98 (0.26)
AUC_{0-}	1.04 (0.29).

Maximum plasma concentrations were 650 ng/ml (range 451-851 ng/ml) following IV administration and 350 ng/ml (range 255-425 ng/ml) following rectal administration. These maxima were reached after 6 minutes (range 2.5-15 minutes) by the IV route and after 18 minutes (range 10-47 minutes) by rectal administration. The differences between the pharmacokinetic parameters in the two studies probably reflect the known wide interindividual variations.

2.4   Interactions

Enhanced sedation or respiratory and cardiovascular depression may occur if diazepam is given with other drugs that have CNS depressant properties (eg. antipsychotics, anxiolytics, sedatives, antidepressants, hypnotics, narcotic analgesics, anaesthetics, antiepileptics) or with agents that interfere with its metabolism by hepatic enzymes (eg. isoniazid, disulfiram, cimetidine, omeprazole, oral contraceptives). Diazepam metabolism is accelerated by theophylline and smoking. Diazepam may interact with other hepatically metabolised drugs causing inhibition (levodopa) or potentiation (phenytoin, muscle relaxants).

3   Clinical trials

Diazepam is a well known compound which has been in clinical use for over 20 years. Many pharmaceutical products with different routes of administration have been authorised for use in the European Community. The therapeutic efficacy of diazepam in the claimed indications and the safety profile of the drug is well known (Gilman et al 1990). Examples of clinical trials in which diazepam was administered by the rectal route are discussed below.

3.1 Efficacy

3.1.1 Trials in seizure disorders

Intermittent treatment of afebrile seizure with rectal diazepam (children and adolescents) (Kruse 1983).

Thirty-eight patients aged 5 months to 18 years with severe seizure disorders (28 with partial epilepsy and 10 with generalised epilepsy) were treated with Diazepam Rectal Tubes, mean dose 0.39 mg/kg (range 0.15-0.7). Rectal application was used for 100 seizure episodes. 70% of episodes could be interrupted within 20 minutes. Improvement (eg decrease of intensity of seizures, decrease of seizure frequency) was reported in eight episodes. In 22% of seizure episodes treatment with rectal diazepam was not effective. In terms of the number of patients, 81% (31) responded well, 16% (6) only partially and 3% (1) not at all. The treatment was generally well tolerated.

Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children (Knudsen 1979)

Forty-four patients aged 6 months to 5 years suffering from febrile convulsions or epilepsy were treated with a rectally applied diazepam solution primarily designated for intravenous use (Apozepam ampoules, 2 ml containing 10 mg diazepam, Apothekernes laboratory, Oslo, Norway). Rectal application was used for 59 seizure episodes. Children aged < 3 years received 0.5 to 0.9 mg/kg diazepam and children aged > 3 years were given 0.6 to 0.8 mg/kg. Efficacy was defined as interruption of the convulsion within 10 minutes of administration.

Rectal diazepam was effective in the acute treatment of convulsions in 80% of cases. In 10% the treatment failed, whereas diazepam given IV had a prompt effect. Another 10% of convulsions were resistant to diazepam irrespective of the route of administration. Early treatment of convulsions (within 15 minutes of onset) was effective in 96% and late treatment in 57% of cases. The treatment was generally well tolerated.

Diazepam rectal solution for the home treatment of acute seizures in children (Hoppu et al 1981)

Seventeen epileptic children aged 11 months to 15 years with a history of prolonged convulsions were given a rectally applied diazepam solution primarily designated for intravenous use (Apozepam ampoules, 2 ml containing 10 mg diazepam, Apothekernes laboratory, Oslo, Norway) for administration at home. An initial dose of 0.5 mg/kg was employed with a maximum of 20 mg per single dose. Rectal application was used for 65 seizure episodes. Efficacy was defined as interruption of the convulsion within 15 minutes of administration.

Rectal diazepam was effective in the acute treatment of convulsions in 80% of cases. Seizure duration was longer than 15 minutes in 12% and longer than 30 minutes in 8%. The treatment was generally well tolerated.

Intrarectal diazepam in epileptic adults (Remy et al 1992)

Thirty-nine patients aged 16 to 65 years suffering from serial epileptic seizures within a refractory epileptic disorder (mostly of frontal lobe origin) were treated with either 20 mg or 30 mg diazepam from a solution primarily designated for intravenous use (Valium

ampoules containing 10 mg diazepam, Roche Laboratories, Neuilly-sur-Seine, France). Twenty-one patients received 20 mg (group 1) and 18 were given 30 mg (group 2). The two groups were homogenous).

Arrest of seizures was achieved in six patients in group 1 (29%) and in 13 patients in group 2 (72%). The threshold level of diazepam in the serum was reported to be between 200 and 300 ng/ml. Onset of clinical effect was noted approximately 10 minutes after instillation. The effective dose was 0.5 mg/kg. The treatment was generally well tolerated.

3.1.2 Trials on sedation

Comparison of sedation, amnesia and patient comfort produced by IV and rectal diazepam (Lundgren et al 1984)

Twenty-seven patients aged 16 to 35 years undergoing oral surgery for removal of impacted third molars were treated in a cross-over study with either diazepam IV or Stesolid rectal tubes. The order of the sedation method was randomised. IV diazepam was titrated at a rate of 2.5 mg/min to a clinical endpoint; the mean dose used was 0.22 mg/kg (range 0.14–0.37 mg/kg). Rectal diazepam was given in a standardised dose of 0.5 mg/kg.

There were no significant differences concerning postoperative recovery time, postoperative need for analgesics, the surgeons' rating of sedation or the side effects. Amnesia was significantly higher during IV administration. Sedative effects after the first operation were rated as good by 87% of patients given IV diazepam and by 75% of those given rectal diazepam. After the second operation, 10 patients (37%) found the level of sedation to be equal, 13 (48%) experienced a stronger sedative effect with IV diazepam and 4 (15%) with the rectal tube.

Serum concentration and drug effect after IV and rectal administration of diazepam (Lundgren 1987)

Seventeen patients aged 17 to 38 years undergoing oral surgery for the removal of impacted third molars were treated in a cross-over study with either diazepam IV or Stesolid rectal tubes. The order of the sedation method was randomised. IV diazepam was titrated to a clinical endpoint; the mean dose used was 0.25 mg/kg (range 0.14–0.45 mg/kg). Rectal diazepam was given initially as a minimum dose of 0.5 mg/kg. Patients who did not respond within 15 minutes were given an additional 10 mg rectally. The mean dose used was 0.53 mg/kg (range 0.5–0.58 mg/kg).

Both the serum concentration and the effect reached their mean peaks at the same time; however, this was 15 minutes later after rectal compared with IV administration. IV use resulted in a higher serum concentration at the clinical endpoint than did rectal administration, but the mean effect levels were equal for both methods. Eleven patients (65%) preferred the rectal sedation, 4 (24%) the IV route and 2 (11%) found the methods equal.

3.1.3 Assessment of efficacy

The administration of Diazepam Rectal Tubes is efficient and simple to use in an emergency and for acute sedation. The clinically desired effect can be achieved within an acceptable period of time when compared to IV administration. Rectal diazepam

solution is faster, more efficient and more reliable than diazepam given by suppositories, oral or IM routes.

3.2 Safety

The safety profile of the compound diazepam is well known. Similar adverse experiences have been reported with different marketed diazepam formulations. These compound-related side effects are listed in the Summary of Product Characteristics. However, the product under discussion is intended to be used at a different site, the rectal mucosa, as opposed to other marketed formulations such as tablets and injections.

3.2.1 Preclinical safety

Preclinical evidence for the local tolerability of the product is derived from four animal studies which are reported in the Pharmaco-toxicological Expert Report. Single and repeated application of diazepam rectal solution 4 mg/ml (Stesolid, Dumex) to the conjunctival sac of the rabbit caused no local irritation. Repeated rectal administration to beagle dogs showed no macroscopic or microscopic changes to the anal mucosa or the rectal ampulla.

3.2.2 Safety in man

In man, the extent of local irritation was studied in 24 healthy adult volunteers in a randomised, triple cross-over design by applying 10 ml diazepam rectal solution (Stesolid, Dumex) v. 2.5 ml diazepam rectal solution (Stesolid, Dumex) v. 2.5 ml vehicle, (Hansen et al 1989).

A burning or stinging sensation lasting up to 15 minutes was reported in 60% of subjects immediately after 10 ml administration, in 12% after 2.5 ml administration and 0% after vehicle administration. Endoscopic assessment 24 hours after instillation showed mechanical irritation in two subjects given 10ml and one given 2.5ml and local irritation, probably caused by diazepam, vehicle or both, in two subjects given 10ml and one each after 2.5ml and the vehicle. Control endoscopy seven days after administration revealed no pathology. The irritation appears to be volume related and it might be expected to affect between 12 and 60% of patients given the usual dose. Slight local irritation may be advantageous in causing hyperalmia and therefore more rapid absorption.

In the clinical trials reported above, very few serious adverse reactions were observed. The reactions reported were typical of those known to occur with diazepam particularly during IV administration.

Respiratory disturbances

One child aged 6 months (5 kg) receiving a dose of 0.7 mg/kg reacted with respiratory depression for one hour. No ventilatory assistance was required. Bronchial hypersecretion was already present during the course of an intermittent grand mal one hour before the application of rectal diazepam, (Kruse 1983).

Another child aged 3 years receiving a dose of 0.55 mg/kg developed respiratory arrest five minutes after instillation of rectal diazepam. Ventilatory assistance was required for some minutes (Hoppu et al 1981).

Spontaneously resolved respiratory disturbances were reported in a 16-year old patient already on phenobarbital who received a dose of 0.5 mg/kg (Hoppu et al 1981).

Although a few cases of respiratory depression have been reported with rectal diazepam, it is considered to be more likely to occur with too rapid administration of intravenous diazepam (Evaskus 1977).

Development of seizures

One patient suffered from a clonic seizure 65 minutes after administration. He was reported to have a temperature of 40°C and a diazepam level of 1185 ng/ml (Knudsen 1977). In another case, a patient suffering from spike wave status epilepticus, the condition was transformed into a series of tonic seizures (Kruse 1983).

Other side effects reported were those usually associated with diazepam and were mild in nature. They were mostly related to the therapeutically desired effects of the drug eg. sedation, muscular hypotonia, drowsiness, etc.

3.2.3 Assessment of safety

The current safety record for rectal diazepam is good. The incidence of systemic adverse reactions is low and the side effects reported are typical for diazepam. The instillation of rectal diazepam is well tolerated locally. No permanent changes at the site of administration have been observed.

4 Post-marketing experience

Diazepam has been available in Europe in a rectal tube formulation since 1978. In the UK the product was first marketed in 1982 under the name Stesolid (Dumex/CP Pharmaceuticals Ltd).

Between November 1985 and March 1994, eight reports of adverse events giving a total of 12 reactions have been reported to the UK CSM referring to Stesolid Rectal Tubes (Dumex). These reports included apnoea (2), respiratory depression (2), respiratory failure (1), hypoxia (1), inability to maintain airway (1), bradycardia (1), gastrointestinal disorder (2), drug interaction (1), hypotension (1). A further eight cases were reported as being unresponsive to treatment.

A total of 1.13 million tubes of 10mg and 2.28 million tubes of 5mg presentation were sold during the period April 1989 to November 1992.

5   Other information

There is no other information.

Conclusion

6.1   Efficacy

The efficacy of Diazepam Rectal Tubes in the claimed indications is comparable to the IV use of diazepam. The advantage of the product is the combination of simplicity of use with a similar rapidity of onset of effect when compared to the IV administration. IV diazepam is an essential emergency medication for the initial treatment of prolonged seizures or status epilepticus. The use of the rectal route has the following advantages:

- it is not restricted by the necessary presence of physicians or suitably skilled nursing staff;
- it can be used by family members or nursing staff without special training;
- it is not restricted to aseptic conditions;
- it is not as difficult to use in the presence of patient movement;
- it does not expose patients to local adverse reactions (eg thrombophlebitis, accidental intraarterial injection, etc);
- it does not endanger patient or doctor due to the presence of sharp needles in seizure situations;
- it avoids unnecessary discomfort, particularly in children.
- it is associated with a lower peak serum concentration and therefore less likelihood of respiratory repression.

Despite the lag time of 10 to 20 minutes to reach 'therapeutic' plasma levels, administration of Diazepam Rectal Tubes may on occasion be faster in achieving the desired clinical effect than IV administration because of delays in the arrival of the physician at the site of emergency, delay in establishing and ensuring a safe IV access and the actual time taken for the injection (diazepam must not be injected faster than 2.5 mg/min to reduce the risk of phlebitis or apnoea).

The dosage depends on individual response, age and weight of the patient. It is recommended to initiate treatment with a dose of 0.5 mg/kg. Higher doses should only be used if the clinical response is inadequate after 10 minutes.

6.2   Safety

The safety profile of the substance diazepam is well known. Similar systemic adverse experiences have been reported with Diazepam Rectal Tubes. Local tolerability of the product was found to be excellent in the preclinical, clinical and post-marketing evaluation.

Side effects

The side effects of diazepam are usually mild and infrequent. The most common side effects are sedation, drowsiness, headaches, muscle weakness, dizziness (with risk of falls in the elderly), ataxia, confusion, slurred speech, tremor, numbed emotions, reduced alertness, fatigue, double vision, anterograde amnesia and a hangover effect. Elderly or

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debilitated patients are particularly susceptible to side effects and may require lower doses. Other effects which may occur rarely are dry mouth, increased appetite, gastrointestinal and visual disturbances, jaundice, urinary retention, hypotension, bradycardia, changes in libido, menstrual disturbances, skin reactions, blood dyscrasias, laryngeal spasm, chest pain, respiratory depression and apnoea.

In susceptible patients, an unnoticed depression may become evident. Paradoxical reactions (restlessness, agitation, irritability, rages, hallucinations) are known to occur with benzodiazepines and are more likely to occur in children and the elderly.

Side effects are generally reversible on reduction of the dose and can usually be avoided by individual tailoring of the dose.

Contraindications and precautions

Contraindications against the use of Diazepam Rectal Tubes are those for diazepam itself, ie. hypersensitivity to benzodiazepines, myasthenia gravis and severe respiratory insufficiency. In addition, Diazepam Rectal Tubes should be used with caution in patients with renal or hepatic dysfunction, chronic pulmonary insufficiency, closed angle glaucoma or organic brain changes, particularly arteriosclerosis. Diazepam should not be used in pregnancy or lactation unless the benefit is considered to outweigh the risk. Use near the end of pregnancy or during labour can be associated with hypothermia, hypotonia, respiratory depression and poor suckling in the neonate.

As with other benzodiazepines extreme caution should be used if prescribing diazepam for patients with personality disorders. The disinhibiting effects of benzodiazepines may be manifested as the precipitation of suicide in patients who are depressed or show aggressive behaviour towards self and others.

Diazepam can affect the reaction capacity sufficiently to impair the ability to drive and operate machinery; this effect is potentiated by the concurrent intake of alcohol.

Dependence potential

Tolerance and dependency may develop with the chronic or repeated use of diazepam even after daily use for only a few weeks. This applies not only to abuse involving particularly high doses but also to usage in the normal therapeutic dosage range but it is not likely with this formulation if used as directed.

Use in pregnancy and lactation

There is no evidence regarding the safety of diazepam in pregnancy. It should not be used especially in the first and third trimesters, unless the benefit is considered to outweigh the risk.

In labour, high single doses or repeated low doses have been reported to produce hypothermia, hypotonia, respiratory depression and poor suckling (floppy infant syndrome) in the neonate and irregularities in the foetal heart.

Diazepam is excreted in the breast milk and therefore its use during lactation should be avoided.

Interactions

Enhanced sedation or respiratory and cardiovascular depression may occur if diazepam is given with other drugs that have CNS depressant properties (eg. antipsychotics, anxiolytics, sedatives, antidepressants, hypnotics, narcotic analgesics, anaesthetics, antiepileptics) or with agents that interfere with its metabolism by hepatic enzymes (eg. isoniazid, disulfiram, cimetidine, omeprazole, oral contraceptives). Diazepam metabolism is accelerated by theophylline and smoking. Diazepam may interact with other hepatically metabolised drugs causing inhibition (levodopa) or potentiation (phenytoin, muscle relaxants).

Overdosage

The symptoms of mild overdose may include confusion, somnolence, ataxia, dysarthria, hypotension, muscular weakness. In cases of severe overdose, depression of vital functions may occur, particularly the respiratory centre (respiratory and circulatory depression, cyanosis, loss of consciousness progressing to the development of respiratory and cardiac arrest). As drug levels fall severe agitation may develop. Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored and supportive measures taken to maintain cardiovascular and respiratory function. Flumazenil is indicated to counteract the central depressive effect of benzodiazepines.

6.3   Risk-Benefit assessment

Diazepam is a well known compound with an established efficacy and safety profile. The absorption of diazepam from the rectal solution is rapid and almost complete leading to therapeutic plasma levels within minutes of an adequate dose. The Diazepam Rectal Tube is easy to handle and can be administered by people without specialist medical training (eg. nursing staff, patient's family members). The rectal tube offers the possibility of relatively safe and easy use of diazepam intended for rapid absorption with a low incidence of local or systemic adverse events. It broadens the therapeutic range of diazepam products providing an alternative route of administration. This is particularly appropriate for patients experiencing epileptic or febrile convulsions in whom the intravenous route may not always be practicable. It may also be a convenient route of administration for preoperative sedation, especially in children.

In my opinion the clinical efficacy and safety of the Diazepam Rectal Tube in the proposed indications and at the proposed dose are well documented and the potential benefits of the product considerably outweigh any potential risks.

Signature of Expert   Place, date

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