AN EVALUATION OF THE USE OF CISAPRIDE IN HORSES WITH CHRONIC GRASS SICKNESS (EQUINE DYSAUTONOMIA)

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SUMMARY

A clinical trial was carried out to determine the effect of cisapride on rate of passage of digesta and clinical parameters in horses with chronic grass sickness. Sixteen horses were given intramuscular cisapride (0.1 mg kg^{-1} three times daily) (group I), and 15 received oral cisapride (0.8 mg kg^{-1} three times daily) (group O). A liquid-phase marker (cobalt-EDTA) and a solid-phase marker (polystyrene pellets) were given by stomach tube at the beginning of each of three consecutive 7 day periods, i.e., before, during and after cisapride therapy. Seven horses in each group completed the rate of passage trial; the remainder provided clinical data only. The rate of passage was found to be significantly faster after cisapride therapy than before. Comparison with data from 20 normal animals showed a trend towards normal rates of passage after therapy. In cases that died during the trial, the caecum and large colon were the main sites of pellet retention. Dry matter intake was significantly higher after therapy than before in group O and dry matter output was higher after treatment than before in both groups. Gut auscultation score increased in both groups in the periods during and after cisapride administration but heart rate was unaffected. Diarrhoea and colic occurred in each group but its occurrence was not associated with cisapride therapy. The results suggest that by increasing gut motility, cisapride is of benefit in the management of selected cases of chronic grass sickness.

KEYWORDS: Horse; autonomic nervous system; grass sickness; gastrointestinal motility; cisapride.

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0007-1935/96/050537-13/$12.00/0

INTRODUCTION

Grass sickness (equine dysautonomia) is a disease of unknown aetiology characterized by degenerative changes resembling chromatolysis in the peripheral autonomic ganglia (Obel, 1955), certain brain stem nuclei (Barlow, 1969) and the plexuses of the enteric nervous system (Doxey *et al.*, 1992; Pogson *et al.*, 1992). The disease occurs in three overlapping forms, acute, subacute and chronic, all of which are characterized clinically by varying degrees of reduction in gastrointestinal motility and dysphagia. Acute cases are severe and die within 2 days of the onset, whereas subacute cases die or require euthanasia within 2–7 days or progress to the chronic form. It is usually considered that the overall mortality exceeds 95%. The situation regarding recovery is unclear because the diagnosis can only be confirmed by histopathological examination of the peripheral autonomic ganglia at *post mortem* examination, or the enteric nervous system at laparotomy.

Gerring & King (1989) described the successful use of the prokinetic agent, cisapride (Reynolds, 1989), in the treatment of equine postoperative ileus. Cisapride is a synthetic substituted benzamide which facilitates acetylcholine release from the postganglionic cholinergic nerves of the myenteric plexus of the gut (Lee *et al.*, 1984; Schuurkes *et al.*, 1985). It lacks the central anti-dopaminergic effects associated with the related, and more commonly used compound in veterinary medicine, metoclopramide (Schuurkes *et al.*, 1987). Because some morphologically normal neurones remain in the myenteric plexus of the gut in chronic grass sickness, cisapride might be of therapeutic benefit in this disease. The purpose of this study was to assess the effect of cisapride on rate of passage of digesta and on other clinical parameters with a view to improving the wellbeing and survival rate of cases of chronic grass sickness.

MATERIALS AND METHODS

Animals

Data were collected from 44 cases of chronic grass sickness referred to the Royal (Dick) School of Veterinary Studies. Eighteen were females, 25 were geldings and one was a stallion. The mean age was 5.5 years (range 1–17). They consisted of nine ponies, seven cobs, 21 pure or crossbred thoroughbreds and seven heavy horses. In the 18 animals that survived, a diagnosis of grass sickness was based on clinical criteria previously described (Milne *et al.*, 1994). The 26 cases that died showed the same clinical signs as the survivors although some signs differed in severity between the survivors and non-survivors (Milne *et al.*, 1994). With the exception of two cases that died at home, the diagnosis was confirmed by histological examination of the coeliacomesenteric, stellate, superior cervical and/or intervertebral ganglia.

The animals had been ill for a mean of 12 days (range 4–30) before the trial started. Eleven had been ill for 4–7 days at the start; thus for the first 1–4 days of the trial, they would have been subacute cases. Those which completed the trial were housed in loose boxes on rubber flooring to allow total faecal collections.

Due to variation in severity of dysphagia, appetite and individual preference, it was not possible to feed a standard diet. Overall, the feeds consumed consisted of grass, hay, soaked sugar beet pulp, alfalfa fibre ("Alfa 'A' ", Dengie Crops Ltd.) alfalfa cubes ('Alfa nuts', Dengie Crops Ltd.), apples, carrots, turnips, bruised oats, rolled barley, pelleted micronized barley, bran, coarse mix ('Cool Mixture', Dalgety Spillers and 'Baileys No. 8', Baileys Horse Feeds), high fibre coarse mix ("Fiber 'P' ", Dodson and Horrell Ltd.), horse cubes, cooked cereal meal ('Baileys No. 1'), milk pellets, molasses, corn oil and 'Newcastle Brown Ale' (Scottish and Newcastle Breweries Ltd.). The feeds most often preferred by the horses were grass, coarse mix, oats and bran.

The grass sickness cases were divided into three groups. Group I consisted of 16 cases which received intramuscular (i.m.) cisapride and group O consisted of 15 cases which received oral cisapride. Of the 16 cases in group I, seven were given markers of rate of passage and completed the trial, six received markers but did not complete the trial and three completed the trial but did not receive markers. The cases that completed the trial but did not receive markers were those kept on straw bedding when the rubber-floored boxes were already occupied. In group O, these numbers were seven, four and four, respectively. A third group of 13 cases was managed in the same way as groups I and O, except that they did not receive cisapride. It was intended to use these animals as a cisapride-untreated control group but it was subsequently found that the five which completed the trial had milder gastrointestinal tract dysfunction than groups I and O. Thus, the data from the untreated cases are not presented except that they were compared with the cisapride-treated groups to assess whether cisapride caused side-effects and eight were used to provide information on the sites of pellet retention in the gut.

In addition, 20 sets of rate of passage data were obtained from normal, untreated horses (eight) and ponies (12) fed diets that consisted of 100% alfalfa (low fibre), 66% alfalfa/33% chopped oat straw, 33% alfalfa/66% chopped oat straw and 100% chopped oat straw (high fibre). This disparate range of diets and animal types was chosen for comparison with the grass sickness cases as the latter ate a variety of foods and differed widely in body weight.

In every case, the aim was to treat the animal successfully and the welfare of the horses was always the first consideration. Thus, cases were never kept alive solely for the purposes of the trial once it had been decided that euthanasia on humane grounds was required; and the few cases that disliked the rubber flooring were moved to straw-bedded boxes. The owners' informed consent was obtained in each case.

Experimental design

The trial consisted of three consecutive 7 day periods. At 09.00 h on the first day (day 0), each animal was given 200 red polystyrene spherical pellets (6 mm diameter) of specific gravity 1.050 (Precision Plastic Ball Co.) and 5 g of cobalt EDTA (CoEDTA) in 250 ml water, by nasogastric tube. The CoEDTA (sodium salt) was prepared as described by Uden *et al.* (1980). Faeces were collected and pooled for each animal every 12 h at 09.00 and 21.00 h, for pellet recovery and analysis of the cobalt concentration. Days 0–7 were designated the 'before' therapy period.

On day 8, 200 blue pellets and a further 5 g CoEDTA were administered and faeces collected as before, until day 14. This was designated the 'during' therapy period. Throughout this period, group I were given i.m. injections of 0.1 mg cisapride per kg body weight three times daily (at 09.00, 15.00 and 22.00 h) for the 7 days and group O received oral cisapride ('Prepulsid', Janssen Cilag Ltd.), at a dose rate of 0.8 mg kg^{-1} three times daily for 7 days. Oral cisapride was administered by crushing 10 mg tablets into a fine powder, suspending it in 20–50 ml of tap water and placing the suspension towards the back of the mouth with a syringe.

Days 15–21 constituted the 'after' therapy period. Two hundred yellow pellets and 5 g CoEDTA were administered at 09.00 h on day 15 and faeces collected every 12 h as before. No other therapy was administered during the trial apart from probiotics and occasional analgesia for mild colic. The latter consisted of flunixin meglumine ('Finadyne', Schering-Plough) or phenylbutazone ('Equipalazone', Arnolds Veterinary Products) administered intravenously (i.v.) at half the manufacturers' recommended dose rate, which was sufficient to produce adequate analgesia. Animals in group N were given pellets and CoEDTA on a single occasion. They did not receive cisapride therapy.

In the animals that required euthanasia before the end of the trial, the number of each colour of pellets in four areas of the gastrointestinal tract was determined i.e. stomach/small intestine, caecum, large colon and small colon/rectum.

The mean daily dry matter intake (DMI) was calculated by recording the wet weight of each feed consumed over each of the three periods of the trial, converting to dry matter consumed and dividing the total DMI for each period by the number of days in that period. The mean daily faecal dry matter output (DMO) was calculated by recording the total faecal output as dry matter for each period of the trial divided by the number of days in each period.

Clinical examination of all grass sickness cases was carried out frequently, but at approximately 13.00 h each day, the nature and audibility of the gut sounds and the heart rate were determined. Auscultation of four sites, the left dorsal, left ventral, right dorsal and right ventral abdominal quadrants, was carried out over several minutes and the sounds scored as follows. Absence of borborygmi was scored as 0, short duration 'mixing' contraction sounds only was scored as 1, 'mixing' contractions plus longer duration peristaltic sounds was scored as 2 (i.e., normal activity) and excessively loud sounds was scored as 3. The score for each site was added to give a total 'auscultation score' which could, therefore, range from 0 to 12. The mean heart rate for each horse during each period was calculated. The horses were checked also at frequent intervals for possible side-effects of cisapride therapy, such as colic or diarrhoea. Blood samples were collected immediately before the start of cisapride therapy (day 8) and on the day after the cessation of therapy (day 15). The samples were analysed for haematological parameters, total serum protein, albumin and globulin.

Analytical methods

The polystyrene pellets were removed manually from each 12 h faecal collection and counted. Thereafter, the faeces were weighed and after thorough mixing by hand in a large bucket, a 100–200 g aliquot was taken. The aliquots were dried at 100°C to enable calculation of the total 12 h faecal DMO. The dried faeces were ground through a 1 mm screen for subsequent cobalt analysis. Cobalt was determined by atomic absorption spectrometry, as described by Uden *et al.* (1980).

Data analysis

For each period of the trial and for each animal, the cumulative number of pellets excreted was plotted against time. From the resulting sigmoid curves, the time from administration to first appearance of the pellets in the faeces (T_0) and the time for excretion of half of the pellets (T_{50}) was calculated. The time from CoEDTA administration to its peak excretion in the faeces was measured for each study phase. Paired *t* tests and Student's *t* tests were used for within- and between-group comparisons, respectively, for both the pellet and cobalt excretion data. The number of pellets of each colour recovered from each of the four areas of the gut at *post mortem* examination was expressed as a percentage of the number of each colour administered (200). These data were unsuitable for statistical analysis. The mean daily DMI, DMO, packed cell volume (PCV), haemoglobin and individual leucocyte types were compared between groups by the Mann–Whitney test and between periods (within groups) by the Wilcoxon Rank test. Auscultation score, heart rate, red blood cell count, total white blood cell count, total serum protein, albumin and globulin were compared between groups and between periods using Student's *t* test and paired *t* tests respectively. The incidence of side-effects was compared between groups by calculating the 95% confidence intervals.

RESULTS

Survival rate

Five of the 16 cases in group I survived (31%), 10 of the 15 cases in group O (67%) and three of the 13 control cases (23%). Those that survived are still alive and in work at the time of writing (after 2–5 years) with the exception of one control case which died at home of undiagnosed colic 6 months after discharge. Of the animals that completed the rate of passage trial, the figures for survival were four out of seven for group I (57%) and seven out of seven for group O (100%).

Rate of passage

The means and standard deviations for the T_0 and T_{50} values for groups I and O before, during and after therapy, and for group N are shown in Table I. T_0 was significantly shorter after i.m. cisapride than before or during treatment in group I ($P<0.01$). The T_{50} values in group I showed similar differences although these were not statistically significant. In group O, T_0 was less after oral cisapride than before treatment ($P<0.02$). T_{50} was significantly less after oral cisapride therapy than before or during the therapy ($P<0.01$ and $P<0.02$, respectively). T_{50} was also less during oral administration of cisapride than before treatment ($P<0.05$). T_0 and T_{50} values did not differ significantly between the two grass sickness groups at any time in the trial. The T_0 and T_{50} values from groups I and O for the 'before' and 'after' periods were compared with the values for group N to determine whether the rate of passage returned to normal after cisapride therapy. T_0 and T_{50}

values were significantly greater than those for group N in groups I and O before cisapride therapy ($P<0.01$ and $P<0.05$, respectively). After cisapride treatment, the T_0 values for groups I and O had improved to the extent that the values were not significantly different from those obtained in normal animals. T_{50} also returned to normal after oral cisapride treatment (group O) but not after injection of cisapride (group I) where the rate of passage of pellets was still significantly longer than normal ($P<0.05$).

The means and standard deviations for the time to peak cobalt excretion are shown in Table II. There were no significant differences in time to peak cobalt excretion between groups I and O during any of the three periods of the trial. However, in both groups, peak excretion occurred significantly earlier after cisapride therapy than before treatment ($P<0.05$ for group I and $P<0.01$ for group O).

Table I

T_0 and T_{50} values (h) for pellet excretion for the 'before', 'during' and 'after' periods [mean and (SD)] in chronic grass sickness cases treated with injectable (I) or oral cisapride (O) and in normal horses (N)

Group		T_0			T_{50}		
		Before	*During*	*After*	*Before*	*During*	*After*
I	7	74^{ae} (43)	50^{b} (19)	34^{ab} (19)	139^{i} (77)	139 (82)	103^{k} (46)
O	7	43^{cb} (17)	38 (26)	22^{c} (5)	146^{dj} (55)	127^{cj} (60)	74^{dc} (50)
N	20	29^{cb} (7)	— —	— —	60^{dk} (14)	— —	— —

Mean values with the same superscript are significantly different.
a,b,d,=$P<0.01$; c,e=$P<0.02$; f=$P<0.05$ (paired t tests).
j=$P<0.01$; g,h,i,k=$P<0.05$ (Student's t tests).
T_0=time to first appearance of pellets in the faeces.
T_{50}=time to 50% excretion of pellets in the faeces.

Table II

Time (hours) from administration to peak excretion (log concentration in faecal dry matter) of CoEDTA for the 'before', 'during' and 'after' periods [mean and (SD)] in chronic grass sickness cases treated with injectable (I) or oral cisapride (O) and in normal horses (N)

Group	n	*Before*	*During*	
I	7	89^{ae} (46)	72^{d} (34)	55^{ae} (14)
O	7	58^{bd} (10)	62 (38)	38^{b} (12)
N	20	31^{cdef} (7)	— —	— —

Mean values with the same superscript are significantly different
a=$P<0.05$; b=$P<0.01$ (paired t tests).
c,d=$P<0.05$; e=$P<0.01$; f=$P<0.001$ (Student's t tests).

The peak cobalt excretion times for the two grass sickness groups were compared with those of normal horses. Group I took significantly longer to achieve peak cobalt excretion than normal animals in all three phases of the trial ($P<0.05$–$P<0.01$) whereas those animals in group O took significantly longer than normal before ($P<0.001$), but not during or after cisapride therapy.

Pellet recovery post mortem

The results for the recovery of pellets from the four areas of the gut at *post mortem* examination of those animals that died during the trial are shown in Fig. 1. The findings suggest that pellets were unlikely to be found proximal to the caecum after the seventh day after administration. Similarly, after 7 days, few were retained in the small colon and rectum and most remaining pellets were found in the caecum and large colon.

Dry matter intake and output

The results of DMI and DMO during each period and for each group are shown in Table III. Group O had a significantly higher intake after than before or during cisapride therapy ($P<0.01$) whereas the intake of group I did not differ between periods. Both groups had a significantly higher DMO after than before or during therapy ($P<0.05$ for group I and $P<0.01$ for group O).

Clinical and laboratory parameters

The mean and standard deviation for the auscultation score in groups I and O for the three periods of the trial are shown in Table IV. There was a highly signifi-

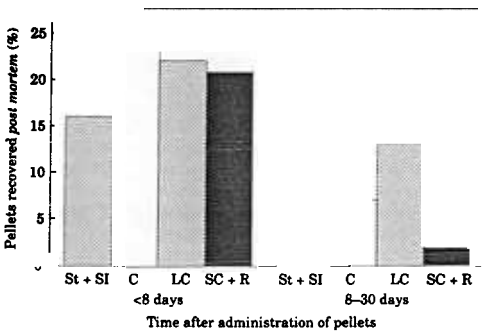

Fig. 1. Percentage of pellets administered which were retained in each of four areas of the gut, less than 8 days (16 sets of pellet data from 14 horses) and 8–30 days after administration (15 sets of data from 8 horses) to chronic cases of grass sickness. Pellets were recovered at *post mortem* examination.
St+SI=stomach and small intestine, C=caecum, LC=large colon, SC+R=small colon and rectum.

cant increase in auscultation score during and after injectable or oral cisapride when compared with the scores before therapy ($P<0.01$–$P<0.001$). Heart rate did not change significantly throughout the trial although the mean values for both groups (49 for group I and 48 for group O) exceeded normal values of 30–45 min^{-1}. The side effects expected to occur were colic and diarrhoea but because these clinical signs are often features of chronic grass sickness, it was necessary to relate their occurrence to therapy. Colic and/or diarrhoea occurred in several cases in groups I, O and the cisapride-untreated cases (data not shown). However, in only a few cases were these signs observed during therapy but not before suggesting that cisapride was not necessarily responsible. The 95% confidence intervals for the incidence of colic or diarrhoea overlapped between the groups for each parameter providing no evidence that cisapride was contributing to their occurrence. However, in some of the cases that already showed a tendency to colic before cisapride therapy, the signs seemed to be exacerbated at approxi-

Table III

Daily dry matter intake (DMI) (median and range) and daily faecal dry matter (DMO) (median and range) in chronic grass sickness cases treated with injectable (I) or oral cisapride (O)

	Group	n*	Before		n*	During		n*	After	
DMI (kg)	I	12	0.92	(0.05–6.89)	12	1.04	(0–7.10)	10	2.08^{c}	(0.05–5.81)
	O	13	2.49^{a}	(0.08–6.36)	13	2.52^{b}	(0–7.79)	11	5.31^{abc}	(0.07–10.35)
DMO (kg)	I	12	0.33^{d}	(0.03–2.58)	12	0.30^{e}	(0–2.68)	10	0.79^{de}	(0.03–2.83)
	O	14	0.52^{f}	(0.05–1.77)	13	0.45^{g}	(0.01–2.03)	10	1.95^{fg}	(0.07–2.60)

Median values with the same superscript are significantly different.
a,b,f,g=$P<0.01$; d,e=$P<0.05$ (Wilcoxon Rank tests).
c=$P<0.05$ (Mann–Whitney test).
*n is less than 16 for group I and 15 for group O because it was not possible to collect all the data from every case.

Table IV

Gut auscultation score for the 'before', 'during' and 'after' periods [mean and (SD)] in chronic grass sickness cases treated with injectable cisapride (I) or oral cisapride (O)

Group	n*	Before	n*	During	n*	After
	15	3.4^{ab} (0.9)	15	5.9^{a} (2.0)	13	5.2^{b} (1.6)
	15	3.7^{cd} (2.1)	15	5.1^{c} (2.2)	12	5.7^{d} (1.9)

Mean values with the same superscript are significantly different
a,d=$P<0.001$; b,c=$P<0.01$ (paired t tests).
*Where n is less than 16 for group I and 15 for group O, it was not possible to collect all the data from every case.

mately 2 h after oral cisapride, the expected time of peak pharmacological effect, and 1–2 h after injectable cisapride.

No significant differences in haematological parameters or serum proteins were observed between periods or between groups and the mean values were within normal limits.

DISCUSSION

Problems associated with the trial

Undertaking a clinical trial with animals suffering from grass sickness presented two problems. First, in those that survived, the diagnosis could not be confirmed because there is no *ante mortem* diagnostic test other than histological examination of small intestinal biopsies obtained at laparotomy. This procedure was unacceptable to owners on grounds of cost, the fact that all cases showed typical signs of the disease and a laparotomy might, in itself, adversely affect the outcome. The case for the correct diagnosis of the disease in survivors on the basis of clinical findings has previously been made (Milne *et al.*, 1994).

The second problem was the difficulty in obtaining animals that had the disease but were not treated with cisapride. A similar situation was encountered by Gerring & King (1989) in their investigation into postoperative ileus; they could not justify a control group on ethical grounds because the beneficial effects of the drug were immediately clear. At the beginning of the current study, cases were randomly assigned to the untreated and treated groups but an obvious and immediate increase in borborygmi and a gradual increase in appetite after just a few days of their treatment with cisapride meant that towards the end of the trial, we could not deny cisapride treatment to animals that required it. Consequently, the five untreated cases which completed the trial were relatively mildly affected, although overall, the untreated group had the worst recovery rate of the three groups (23%). This could indicate also that for animals to survive without treatment, they must be relatively mildly affected, and that therapy therefore, influenced outcome. In the absence of a satisfactory control group, it could be argued that the improvement in gut motility after therapy occurred because the animals were improving with time, independent of cisapride therapy. However, this was unlikely because the cisapride-treated cases that died during or after the trial also showed improvement in gut sounds and rate of passage.

Choice of markers

A variety of markers have been used to assess the transit time of digesta. CoEDTA is a suitable liquid-phase marker as it is poorly absorbed from the gut and the percentage recovered is high (Uden *et al.*, 1980). Chromium-mordanted hay fulfils the criteria required of a solid-phase marker (Uden *et al.*, 1980; Cuddeford & Hughes, 1990), and is preferable to particulate markers such as polystyrene pellets. The latter can be used to yield information on relative but not absolute rates of passage (Uden *et al.*, 1980). Grass sickness cases refused to eat milled, Cr-mordanted hay, and the material proved impossible to administer as a single dose by nasogastric tube. A preliminary study in normal horses and ponies

showed that polystyrene pellets were consistently excreted slightly more slowly than Cr-mordanted hay (unpublished data) conforming the findings of Uden *et al.* (1980). It was not possible to express the rate of passage data in the same way for both the solid- and liquid-phase markers. Cumulative excretion curves could not be calculated for the liquid-phase marker and peak excretion time could not be calculated for the solid-phase marker for the grass sickness groups. Although time to peak pellet excretion was measurable in group N, in the grass sickness cases, the pellets tended to be excreted in batches. This is an undesirable property for a marker of digesta passage, and probably occurred in the grass sickness cases because of abnormal gut motility.

Major findings of the study

The major finding was that markers indicating the relative rates of passage of both the solid and liquid phases of the ingesta were excreted significantly faster after either injectable or oral cisapride therapy compared with the pretreatment periods. During the period of cisapride administration, the results were variable and in general, there were few significant differences between the pretreatment and treatment periods. There was evidence of a return to normal values for T_0 and T_{50} for the solid-phase marker and, at least in group O for the liquid-phase marker, after therapy.

The improvement in rate of passage was more clear-cut for the cases receiving oral rather than injectable cisapride, and because more of the orally-treated cases survived, it could be argued that the prognosis was improved by oral therapy. Care is needed when comparing groups O and I because it was not possible to measure the plasma levels of cisapride which may have been higher after oral administration (0.8 mg kg^{-1}) than after i.m. injection (0.1 mg kg^{-1}). Whilst the i.m. dose rate was based on previous studies (King & Gerring, 1988), a suitable oral dose was arrived at by trial and error in several cases by gradually increasing the dose until there was an obvious increase in borborygmi, similar to those after i.m. administration.

Cisapride is a substituted benzamide, and is an indirect cholinomimetic that facilitates acetylcholine release by acting on postganglionic, cholinergic nerves (Schuurkes *et al.*, 1985) at the level of the myenteric plexus (Lee *et al.*, 1984). The effect of cisapride on normal fasting gut motility has been investigated in ponies by King & Gerring (1988). They found that gastric and colonic contractile activity increased and that there was an increase in rate and amplitude of irregular spiking activity in the small intestine. In an experimental equine postoperative ileus model, Gerring & King (1989) showed that cisapride was effective in restoring electromechanical activity, coordination between gastric and small intestinal contractions and rate of passage of solid-phase markers; because of this they suggested the potential therapeutic value of cisapride in grass sickness cases. In the current study, the increase in rate of passage, presumably as a result of increased gut motility in cisapride-treated grass sickness cases is, therefore, likely to be associated with the facilitation of acetylcholine release from those cholinergic pathways that were still viable after neurotoxic damage. The fact that rate of passage of ingesta was not consistently significantly faster during cisapride therapy suggested that there might be a delay between administration and the improvement

in coordinated activity. This may reflect a delay of several days before steady-state plasma cisapride levels are reached, as has been shown to occur in man (Van Peer & Verlinden, 1988).

In the cases from which pellets were recovered from the gut at *post mortem* examination, it was found that the caecum and large colon were the main sites of pellet retention. In normal ponies, the major site of retention of particulate markers of digesta flow is the large colon (Argenzio *et al.*, 1974) but retention at this site was abnormally prolonged in the cases reported here. The caecum was not shown to be a site of retention of markers in normal ponies (Argenzio *et al.*, 1974), and it would appear that caecal activity was severely impaired in fatal chronic grass sickness cases. The degree of neuronal damage in the intramural plexuses of the caecum has only been reported in three chronic cases of grass sickness (Scholes *et al.*, 1993). They found minimal or no enteric neuropathy but only one site in the caecum was sampled and the number of cases investigated was small.

The results for faecal DMO were similar to those of the rates of passage in that group I and group O produced more faeces after cisapride therapy than before or during therapy. The results were less clear cut for DMI with only group O showing a significantly greater intake after than before or during therapy although a similar trend was shown by group I. Whether the improvement in appetite and faecal output contributed to the improved rates of passage after therapy or was the result of it is not certain although the latter seems more likely because increased gut activity, detected by auscultation, was obvious immediately on commencing cisapride therapy, preceding the increase in intake and faecal output. The increased sounds were most obvious approximately 2 h after oral cisapride and 1–2 h after injectable cisapride. This was similar to the results of De Geest *et al.* (1991) who detected increased borborygmi within 3 h of i.m. cisapride in horses at risk of postoperative ileus. It was notable that the increase in gut sounds was maintained in the treated groups even after cisapride therapy stopped (i.e. in the 'after' therapy period) and in most cases, including those which did not subsequently survive, this was maintained after the end of the trial period.

Cisapride had no effect on heart rate despite the fact that horses are thought to be relatively sensitive to its cardiovascular effects and an increase in heart rate has been recorded in normal ponies receiving i.v. cisapride (King & Gerring, 1988). The occurrence of colic or diarrhoea did not appear to be associated with cisapride therapy. Any colic observed was mild and was usually self-limiting or responded to the administration of phenylbutazone or flunixin meglumine at a dose rate lower than that recommended by the manufacturers.

Haematological parameters and serum protein concentrations were recorded before and after cisapride therapy in groups I and O in view of the observation that a marked fall in PCV occurred in two treated cases of postoperative ileus (Gerring & King, 1989). However, no such changes occurred in our study and none has been reported in man (Verlinden *et al.*, 1988).

CONCLUSIONS

The results of the current study support the conclusion that cisapride, administered i.m. or orally, has a beneficial effect on gut motility in cases of chronic grass

sickness, although its effect on the ultimate recovery rate is uncertain. At the time of writing, cisapride is only available as an oral preparation. Although the drug was only administered for 7 days, the improvement in clinical parameters in the surviving cases appeared to be maintained after cessation of therapy. Selection of appropriate cases for treatment is very important (Milne *et al.*, 1994) and other aspects of management including feeding and nursing (Milne & Wallis, 1994) should not be ignored because cisapride therapy without attention to additional managemental factors is unlikely to be successful in effecting a recovery from chronic grass sickness.

ACKNOWLEDGEMENTS

The authors wish to thank the veterinary practitioners who referred the cases, the R(D)SVS clinical and nursing staff who assisted in their care and the owners for allowing their horses to take part. The R(D)SVS Clinical Laboratory analysed the blood samples and Mrs R. Muirhead carried out the cobalt analyses. The work was funded by the ADRA Equine Grass Sickness Fund.

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(Accepted for publication 15 May 1995)