

Cisapride reduces neonatal postoperative ileus: randomised placebo controlled trial

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Abstract

Aim—To assess the efficacy of cisapride in reducing ileus persisting to the tenth postoperative day after neonatal abdominal surgery.

Methods—A prospective, randomised, double blind trial comparing rectal cisapride (1.4–2.3 mg/kg/day) with placebo over seven days was undertaken in 33 neonates.

Results—Seven of 12 (58%) patients receiving placebo and eight of 11 (73%) receiving cisapride achieved a first sustained feed during treatment. Of those receiving cisapride, the first sustained feed occurred at 2.3 days (SEM 0.6) compared with 4.7 days (SEM 0.8) with placebo. By the seventh day the mean daily net enteral balance was 69 (SEM 18) ml/kg in the cisapride subgroup and 17 (SEM 8) ml/kg for those receiving placebo. Stool was passed on 6.3 (SEM 0.4) treatment days in the cisapride subgroup compared with 4.1 (SEM 1.0) treatment days in the placebo subgroup.

Conclusion—Cisapride is effective in neonates with a prolonged ileus after abdominal surgery.

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Keywords: cisapride; gastroschisis; postoperative ileus; prokinesis

Prolonged functional intestinal obstruction complicates the postoperative management of some neonates after the surgical correction of gastroschisis, intestinal atresias, and malrotation. Although parenteral nutrition has revolutionised the care of these children, the longer it is required the greater are the risks of cholestasis and sepsis.¹ Furthermore, longer periods in hospital have financial and social implications. Postoperative ileus is often the major factor contributing to the length of hospital stay.

The prokinetic agent cisapride (Prepulsid; Janssen Pharmaceutical Ltd), a substituted piperidinyl benzamide, is believed to work by enhancing the release of acetylcholine from the myenteric (Auerbach's) plexus. This is based

on experiments with tetrodotoxin, a nerve blocker, and the anticholinergic agent atropine, both of which prevent cisapride induced prokinesis.² Cisapride is at least comparable with metoclopramide in reducing gastric to caecal transit times in adults³ and is effective in adults with normal intestines in the immediate postoperative period⁴ and at 48–72 hours.^{5,6} Its effectiveness in neonates, however, has not been studied. Cisapride is more effective than metoclopramide in improving the oesophageal clearance of refluxed acid and in increasing lower oesophageal sphincter tone in gastro-oesophageal reflux in infants.⁷ It decreases duodeno-gastric reflux⁸ and is used to treat delayed gastric emptying, particularly in diabetes.⁹ Cisapride also has a prokinetic action on the small and large intestine¹⁰ and has been used in idiopathic pseudo-obstruction,¹¹ and in dysmotile neonatal small bowel.¹² Cisapride does not have the antidopaminergic effects of extrapyramidal reactions and prolactin release which are seen with metoclopramide or domperidone.

We therefore wished to determine if there was measurable benefit from the use of cisapride in the management of prolonged postoperative neonatal ileus.

Methods

Neonates over 32 weeks of gestation who had undergone gastrointestinal or abdominal wall surgery and who had a persisting ileus on the tenth postoperative day were entered into the study. Written informed parental consent was obtained and the study was approved by the local ethics committee. Ileus was diagnosed if no enteral feed was being given because of persisting green nasogastric aspirates. Patients were randomly allocated to receive placebo or cisapride in a double blind manner. Patients were removed if they developed mechanical obstruction, necrotising enterocolitis (NEC), or serious cardiovascular, renal, or neurological disorders. Cisapride was given for seven days using 3 mg suppositories. The dose regimen was as follows: neonates of 1.3–2.1 kg received half a suppository every 12 hours (1.4–2.3 mg/kg/day); neonates of 2.1–3.2 kg received half a suppository every 8 hours (1.4–2.0 mg/kg/day); and neonates between 3.2–4.2 kg received one suppository every 12 hours (1.4–1.8 mg/kg/day). Cisapride and placebo suppositories were supplied by Janssen Pharmaceutical Ltd. As enteral feeds were progressively increased parenteral nutrition was decreased. Records of daily enteral intake,

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Table 1 Characteristics mean (SEM) of cisapride and placebo groups

	Rectal cisapride (n=11) 1.4–2.3 mg/kg/day	Rectal placebo (n=12)
Gestation (weeks)	37 (0.4)	37 (0.4)
Birthweight (kg)	2.6 (0.16)	2.5 (0.12)
Aspirate volume on the day preceding treatment (ml/kg/day)	12 (3.5)	11 (2.3)

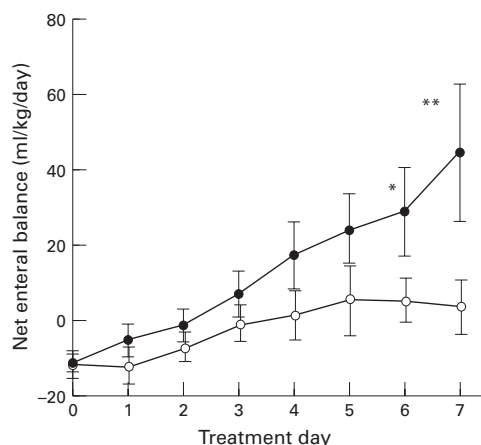


Figure 1 Graph of mean net enteral balance in ml/kg/days for days 1–7 for cisapride • (1.4–2.3 mg/kg/day) (n = 11) or placebo ○ (n = 12) in 23 neonates. Day 0 is the 10th postoperative day after abdominal surgery with persisting ileus. Error bars are standard errors. *P < 0.04; ** P = 0.02; t test.

total daily discarded nasogastric aspirates, and the passage of stool were prospectively recorded. A first sustained feed was defined as the first feed that led progressively to full enteral feeds. After seven days of treatment the trial was concluded and patients were managed as seen fit by their individual clinicians.

Statistical analysis was performed blind. Student's t test was used to assess the difference in the means of normally distributed data.

Results

Thirty three neonates were entered into the study but 10 were withdrawn from analysis: four had not met the entry criteria as they received feeds on the tenth postoperative day; five patients completed the seven days of treatment but were subsequently found to be mechanically obstructed; and one receiving cisapride developed necrotising enterocolitis on treatment day 4. Four of the five mechanical obstructions occurred at intestinal anastomoses, three were related to resected atresias in gastroschisis, and one to a resection for multiple small bowel atresias. One further patient who had had gastroschisis requiring a silo developed intestinal strictures.

Of the remaining 23 patients, 12 received placebo and 11 cisapride. Nineteen had had gastroschisis (all primarily closed), one patient receiving placebo had had duodenal stenosis and another had had multiple small bowel atresias; in each group there was one patient who had had jejunal atresia. The two groups were comparable for gestation, birthweight, and the volume of aspirates on the tenth post-

Table 2 Characteristics mean (SEM) of cisapride and placebo subgroups who attained a first sustained feed during treatment

	Rectal cisapride (n=8) 1.4-2.3 mg/kg/day	Rectal placebo (n=7)
Gestation (weeks)	37 (0.4)	37 (0.3)
Birthweight (kg)	2.66 (0.22)	2.58 (0.16)
Aspirate volume on the day preceding treatment (ml/kg/day)	10.4 (4.3)	12.3 (3.1)

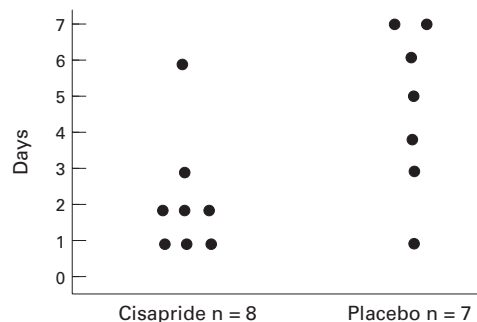


Figure 2 Scattergram of time from start of treatment to first sustained feed for neonates receiving rectal cisapride mean 2.3 days (SEM 0.6) and placebo mean 4.7 days (SEM 0.8) P < 0.029; two tailed t test.

operative day (table 1). The mean aspirate volumes/kg during the seven treatment days did not differ significantly. Both the daily and cumulative feed volumes/kg and the number of days on which stools were passed were consistently better with cisapride. The net enteral balance/kg was greater in the cisapride group than the placebo group, reaching significance at the 5% level on days 6 and 7 (fig 1).

Seven of 12 (58%) patients receiving placebo and eight of 11 (73%) receiving cisapride achieved a first sustained feed during the seven treatment days. Analysis of these subgroups showed that they were comparable with respect to gestation, birthweight, and the volume of aspirates on the 10th postoperative day (table 2). Five (71%) of the placebo subgroup and five (62%) of the cisapride subgroup received breast milk while the others received Pepti-Junior (Cow and Gate). In both subgroups one neonate had jejunal atresia and in the placebo subgroup a further neonate had multiple small bowel atresias; the other 12 neonates had gastroschisis. The cisapride subgroup had a first sustained feed at a mean of 2.3 days (SEM 0.6); in the placebo subgroup the mean was 4.7 days (SEM 0.8) (P<0.029 two tailed t test) (fig 2). From the second treatment day the mean daily net enteral balance was positive and

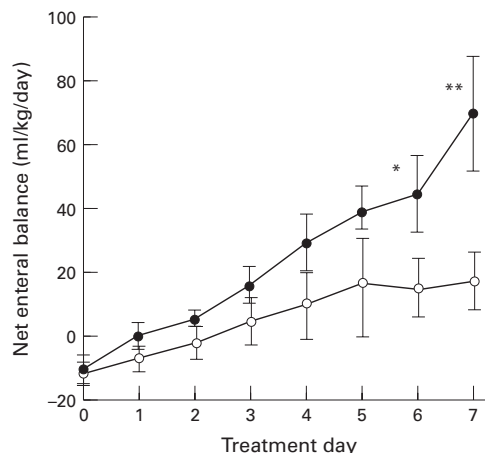


Figure 3 Graph of mean net enteral balance in ml/kg/day for days 1–7 for neonates receiving cisapride • (1.4–2.3 mg/kg/day) (n = 8) or placebo ○ (n = 7) in 15 neonates who attained a first sustained feed. Day 0 is the 10th postoperative day after abdominal surgery with persisting ileus. Error bars are standard errors. *P < 0.04; ** P < 0.02; t test.

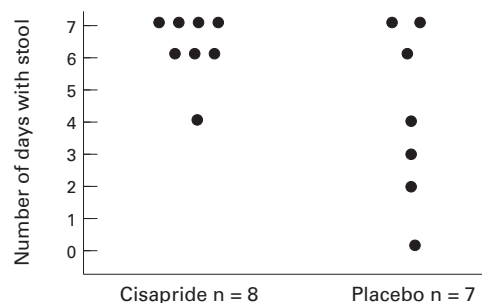


Figure 4 Scattergram of number of days on which stool was passed in neonates who attained a first sustained feed on rectal cisapride mean 6.3 days (SEM 0.4) and placebo mean 4.1 days (SEM 1.0); $P = 0.059$, two tailed t test.

greatest in those receiving cisapride (fig 3), such that by the seventh treatment day it was 69 (SEM 18) ml/kg for cisapride and 17 (SEM 8) ml/kg for placebo ($P < 0.02$; t -test). The average number of treatment days on which stool was passed was also greatest in the cisapride subgroup (6.3 (SEM 0.4) days) compared with placebo (4.1 (SEM 1.0) days) ($P = 0.059$; two tailed t test) (fig 4).

Discussion

We have shown that in postoperative neonatal ileus seven days of rectal cisapride (1.4–2.3 mg/kg/day) started after the 10th postoperative day, increased the net enteral balance, decreased the time to the start of successful feeding, and decreased the number of days without stool.

The number of neonates enrolled in this study was small and the treatment period was brief. This precluded an analysis of the risks of hepatic dysfunction and the length of hospital stay. One neonate receiving cisapride developed necrotising enterocolitis and this has been reported as a possible serious adverse effect.

Importantly, the two subgroups were comparable for the number receiving breast milk which is known to promote faster gastric emptying than formula feeds.¹⁵ Furthermore, the neonate who had had multiple small bowel atresias and who received placebo did exceptionally well, having a net enteral balance of 64 ml/kg/day by day 7, and thus does not contribute to the poor performance of the placebo group. Indeed, if the analysis were limited to those with gastroschisis alone, the benefit of cisapride is more apparent. Although those in the cisapride group were discharged on average sooner than those in the placebo group, the observation is uninformative because at the end of the trial double blinded rectal medication was stopped. Some, but not all, patients in both groups then went on to receive oral cisapride.

Our series consisted, in the main, of patients with gastroschisis but included those with intestinal atresias. Some patients have a prolonged ileus after a Ladd's procedure for duodeno-jejunal malrotation. We have already shown that intestinal dysmotility is associated with operated malrotation,¹⁴ and we would expect such patients to respond to cisapride.

Only a few studies of prokinetic agents in neonates or infants have been carried out.

Erythromycin is prokinetic in the stomach and small bowel, acting through motilin receptors upstream of a cholinergic pathway,¹⁵ and in the ileum via a cholinergic and opiate independent calcium channel pathway,¹⁶ but no colonic effect has been shown.¹⁷ In adults erythromycin improves gastric emptying,^{18–19} decreases oro-caecal transit times in diabetics,^{9, 20} and has been used in pseudo-obstruction.²¹ In children,²² extremely low birthweight neonates,²³ and premature neonates²⁴ erythromycin may improve gastric emptying. Furthermore, erythromycin has been used successfully in postoperative intestinal dysmotility.²⁵ However, these neonatal studies lacked adequate control groups. Erythromycin does not decrease the period of normal postoperative ileus in adults compared with placebo,²⁶ but this brief ileus may well be somewhat different from the prolonged ileus of pseudo-obstruction or that seen in neonates after gastroschisis closure or the resection of intestinal atresias.

Metoclopramide doubles gastric emptying in infants with gastroparesis after abdominal surgery but is reported to have had no effect on seven premature neonates.²⁷

There is growing evidence for an association between a lengthening of the electrocardiographic QT interval and high doses of cisapride. The recommended safe maximum oral dose is now 0.8 mg/kg/day.^{28–30} We used rectal cisapride, the bioavailability of which is around 40% of that of an oral dose.³¹ We therefore expect 2 mg/kg/day to be a safe maximum rectal dose. Cisapride should not be used with erythromycin, clarithromycin, fluconazole, itraconazole, ketoconazole or miconazole, because these agents inhibit the metabolic inactivation of cisapride.

We consider that a study comparing erythromycin with cisapride in postoperative neonates might give us further information, and we are keen to establish if continued management with cisapride significantly shortens hospital stay. Furthermore, the possible benefit of an earlier introduction of prokinetic agents in the postoperative period might be addressed.

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