Randomised controlled trial of cisapride in feed intolerance in preterm infants

Alma Enriquez, Srinivas Bolisetty, Sanjay Patole, Paul A Garvey, Peter J Campbell

Abstract

***Aim*—To assess the efficacy of cisapride in reducing the time required to establish enteral feeds in preterm infants.**

***Methods*—A randomised, double blind, placebo controlled trial was conducted of 34 infants of ⩽ 32 weeks of gestation, assigned to receive either cisapride 0.2 mg/kg/dose four times daily (n=18) or placebo (n=16).**

***Results*—The time taken by the babies to tolerate full enteral feeds was not significantly different between the groups (median 9.5 days *vs* 10 days). There was a significantly lower incidence of large gastric residuals and regurgitation in the treated group compared with the placebo group. The number of episodes of large gastric residuals per infant was also significantly less. No adverse effects were noted.**

***Conclusion*—The routine use of cisapride in preterm infants cannot be recommended to decrease the time to establish enteral feeds. Its use may be justified for clincally significant gastric stasis or regurgitation.**

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Despite growing knowledge in the development and physiology of the immature human gut, management of feed intolerance in low birthweight preterm babies still remains a major challenge to clinicians. The time to achieve full feeding in preterm infants is partly determined by host factors such as lower oesophageal sphincter pressure, gastric emptying time, and motility of the gut.[1]

Cisapride is a first line gastrointestinal prokinetic agent for treating motility disorders in children.[2] In children it can stimulate oesophageal contractility, increase lower oesophageal sphincter pressure, reduce gastro-oesophageal reflux, enhance gastric emptying time, and reduce the whole gut transit time.[2 3] In an uncontrolled trial, Janssens *et al*[4] studied the efficacy of cisapride in 20 preterm infants of less than 34 weeks of gestation. They showed a significant reduction in gastric residuals after 48 hours of treatment with cisapride. Feeding volume was also significantly increased during that period.

We conducted a randomised, double blind, placebo controlled trial to evaluate the efficacy of cisapride in improving feed tolerance in preterm infants of less than 33 weeks gestation at birth. We hypothesised that cisapride would decrease the time required to establish full enteral feeds.

Methods

The study was conducted at the Royal Hospital for Women from May 1994 for a period of 12 months. Informed consent was obtained from the parents of the infants. The study was approved by the hospital research ethics committee. Preterm infants with a gestational age of ⩽ 32 weeks were eligible for the study. Exclusion criteria were: major congenital malformations; birth asphyxia with a 5 minute Apgar score of less than 3; the presence or history of necrotising enterocolitis; confirmed sepsis; organic abdominal illness; and periventricular haemorrhage greater than grade 1.

The end point used for sample size calculation was the time to reach full feed based on our previous 12 month infant population. We aimed for a 40% reduction in the end point with a power of 0.80 and a significant p value of < 0.05. This required a sample size of 32 infants.

The decision to introduce feeding was made by the attending neonatologist. The general policy of the unit is to feed the infant when he/she meets the following criteria: (i) no significant acute respiratory problem and no or minimal ventilatory support (FIO_2 of less than 0.25 and mechanical ventilation rate less than 20); and (ii) haemodynamically stable and not requiring any inotropic medication. After enrolment each infant was randomly assigned to receive either cisapride or placebo by a double blind parallel group design in blocks of 10. The medication code numbers were contained in sealed envelopes. Randomisation coding, cisapride, and placebo preparations were supplied by Janssen-Cilag Pty Ltd. The placebo was prepared using the same bases as used in cisapride.

Cisapride or placebo was given at a dose of 0.2 ml/kg/dose (cisapride was supplied as 1 mg/ml suspension) four times daily, from the time feeds were started. Each dose was given half an hour before the feed. The babies were fed either expressed breast milk or formula milk. The feeding policy was uniform in all the babies; they were fed using a nasogastric tube every 2 hours and feeds were increased by 1 ml every 12 hours if tolerated. The babies were kept prone, with the head of the cot raised, and minimally handled for 1 hour after the feeds.

Gastric aspirates were measured every 6 hours before the feed. A gastric aspirate of greater than 30% of the previous 6 hour feed volume was regarded as significantly large. Abdominal girth was measured at 12 hour

Department of Newborn Care, Royal Hospital for Women, Randwick New South Wales 2031, Australia
A Enriquez
S Bolisetty
S Patole
P Garvey
P Cambell

Correspondence to:
D. Peter Campbell.

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Table 1 Clinical characteristics

	Cisapride (n=18)	*Placebo (n=16)*
Birth weight (g)	1299 (290)	1174 (363)
Gestation (weeks)	28.8 (1.9)	28.4 (2.1)
Male	12 (67)	10 (63)
Hyaline membrane disease	9 (50)	8 (50)
5 min Apgar	8.0 (0.9)	7.7 (1.2)
Mechanical ventilation	12 (67)	14 (88)
PDA	2 (11)	3 (19)
Indomethacin	2 (11)	3 (19)
Theophylline	15 (83)	15 (94)
UAC	6 (33)	5 (31)
Breast milk	17 (94)	14 (88)
Age at trial start (days) Median (range)	4.0 (1-12)	4.0 (1-17)

Mean (SD) are shown. UAC: unbilical arterial catheter. Percentages are shown in paretheses.

intervals before feeds. An increase in abdominal girth of greater than 1.5 cm between the 12 hour intervals was considered abnormal. Any episodes of vomiting/regurgitation and bile stained aspirates during the study were recorded. Reaching full enteral feeds was defined as tolerating a 24 hour volume of 150 ml/kg/day. The duration of total parenteral nutrition required by the babies was noted.

In each subject the trial drug was stopped one week after the attainment of full (150 ml/kg/day) enteral feeds. Infants were monitored for previously reported side effects including liver function abnormalities[4] and sinus tachycardia.[5] All subjects were continuously assessed on cardiorespiratory monitors. Electrocardiographic and liver function tests were performed both at the beginning and on completion of the study.

Statistical analysis was performed using Student's *t* test, Fisher's exact test, and the Mann-Whitney U test, where appropriate. The level of significance was set at $p < 0.05$.

Results

Twenty and 19 babies were enrolled in the cisapride and placebo groups, respectively. Five infants were excluded from the study (two in the cisapride and three in the placebo group) as their feeds were interrupted for the following reasons. In the treated group one infant developed feed intolerance secondary to sepsis with ileus on abdominal *x*-ray picture and was treated with intravenous antibiotics for 7 days; the second baby developed recurrent patent ductus arteriosus and was transferred to another hospital for ductal ligation. In the placebo group one baby developed necrotising enterocolitis and required surgery. Two babies developed persistent regurgitation on days 5 and 7 of the trial, respectively. These two babies were withdrawn from the study at their parents' request and were treated with cisapride after a clinical diagnosis of gastro-oesophageal reflux. Regurgitation ceased after open treatment with cisapride. Their results were excluded from the analysis.

Eighteen babies in the cisapride group and 16 in the placebo group completed the study. The clinical characteristics of the infants at study entry are summarised in table 1. No significant difference was found between the groups for any of the variables.

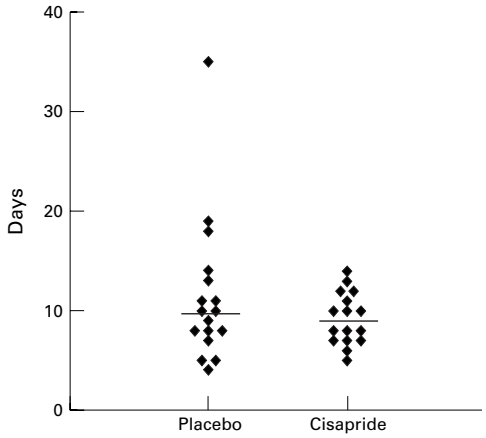

Figure 1 Days to reach full enteral feed for infants receiving cisapride or placebo. Medians are shown as solid bars for each group.

Table 2 Results of the outcome and the symptoms of feed intolerance

	Cisapride	*Placebo*
Days to full feeds	9.5 (5-14)	10 (4-35)
Days on TPN	9.0 (0-20)	8.5 (0-28)
No (%) patients with:		
Gastric residuals > 30%	11 (61)	15 (94)*
Regurgitation	2 (11)	8 (50)*
Bile in aspirates	2 (11)	5 (31)
Abdominal distention	2 (11)	5 (31)
No episodes per patient:		
Gastric residuals > 30%	2 (0-9)	4 (0-17)*
Regurgitation	0 (0-5)	0.5 (0-4)
Bile in aspirates	0 (0-1)	0 (0-19)
Abdominal distention	0 (0-1)	0 (0-3)

Values are medians (ranges). Mann-Whitney test and Fisher's exact test were used. TPN: total parenteral nutrition.
* $p < 0.05$.

Figure 1 shows that there was no significant difference between the two groups in the number of days taken to reach full feeds. The treated group took a median of 9.5 days (range 5 to 14 days) compared with 10 days (range 4 to 35 days) in the placebo group. One particular infant in the placebo group took 35 days to tolerate full enteral feeds due to intermittent regurgitation, increased gastric residuals, and occasional bile stained aspirates.

In the cisapride group 7 (39%) infants had no significant gastric residuals throughout the study period compared with one (6%) placebo infant who remained free of clinically significant gastric aspirates ($p = 0.04$). The treated group showed a significant decrease in the incidence of regurgitation compared with that of the placebo group; two (11%) in the treated group compared with eight infants (50%) in the placebo group developed regurgitation ($p = 0.02$).

The treated group had significantly fewer episodes of large gastric residuals during the study period than the placebo group (median (range), 2 (0–9) *vs* 4 (0–17); $p = 0.01$). There was a trend towards less regurgitation in the treated group, though it did not reach significance (table 2). There was no significant difference in the number of infants who had bile aspirate or abdominal distension between the two groups. The duration of total parenteral nutrition received by the treated

group was similar in both groups (9.1 + 5.2 *vs* 10.2 + 8.2 days, respectively).

None of the infants in the cisapride group developed cholestatic jaundice. Liver function tests at the start and on completion of the study were normal. Sinus tachycardia was not noted during the study period. ECGs obtained at the beginning and the completion of the study showed no rhythm disturbances. The mean QT intervals at the beginning and end of the study were within normal range for age.

Discussion

Many low birthweight premature babies will have feeding difficulties due to various factors related to their gut immaturity. Some of these factors include lower oesophageal sphincter pressure, delayed gastric emptying, and prolonged gastrointestinal transit time.[1] Consequently, when these babies are fed by nasogastric tube, they often develop feed intolerance that is usually manifest by gastric aspirates, regurgitation, bile stained aspirates and/or abdominal distension. They may take several days to weeks to tolerate enteral feeds and are subjected to lengthy periods of parenteral nutrition.

Cisapride is a gastrointestinal prokinetic agent that acts by releasing acetylcholine from the nerve terminals of the gut. In children it increases lower oesophageal sphincter pressure,[6] enhances gastric emptying,[7–9] and increases intestinal transit time.[10 11] It has been widely used in children for a variety of conditions including gastro-oesophageal reflux,[6 12 13] intestinal pseudo-obstruction,[14 15] and constipation.[16 17] It is well tolerated by most children.[2 3]

There is no published evidence to suggest what percentage of gastric residuals should be considered significant in planning the feeding regimen in preterm babies. In our nursery we regard as clincally significant gastric residual volume of greater than 30% of the previous 6 hour feed volume, and the same policy was followed in the study. There were significantly fewer infants with large gastric residuals in the treated group. The number of episodes of large gastric residuals in each infant was also significantly less in the group receiving cisapride. The decrease in the incidence and frequency of large gastric residuals suggests that cisapride may enhance gastric emptying and thereby reduce gastric stasis in preterm babies. These findings correlate with those from the study by Janssens *et al*.[4] They studied 20 preterm neonates with an average gestational age of 26–34 weeks and noted a decrease in the percentage of gastric residuals by over 70%, as well as an increase in feeding volume during 48 hour treatment with cisapride. They studied each baby for three days but they were not placebo controlled.

Our findings suggest that cisapride reduces the incidence of regurgitation in preterm babies. Only two out of 18 babies had an episode of regurgitation in the cisapride group compared with eight out of 16 babies in the placebo group. The lower oesophageal sphincter pressure is less in preterm babies and it can lead to vomiting or regurgitation.[18 19] Cisapride increases the lower oesophageal sphincter tone as well as the amplitude and duration of peristaltic waves in infants with gastro-oesophageal reflux disease.[6] A similar action of cisapride could explain the decrease in the incidence of regurgitation in our study. The mean episodes of regurgitation in each baby were also less in the cisapride group but failed to reach significance, probably because of sample size. Similarly, there was a trend towards a reduction in both the incidence and frequency of bile stained aspirates and abdominal distension in the cisapride group.

Despite some improvement in the symptoms, as mentioned above, the primary end point of decreasing the time to establish feeds was not achieved in the cisapride group. There was only a half day difference between the two groups in the median time taken to reach full feeds. These findings suggest that several other host factors, in addition to lower oesophageal sphincter tone and gastric stasis, on which cisapride may have no effect, determine enteral feed tolerance in preterm infants. These may include immaturity at several levels of the gastrointestinal system including propulsive activity and digestive and absorptive capacity of the gut.[20]

Cisapride was well tolerated by all the infants in the study. Janssen *et al* [4] studied the long term side effects of cisapride at a dose of 0.6 mg/kg/day in 20 preterm infants of less than 34 weeks gestation. Cholestasis developed in four infants and this coincided with an outbreak of candida. In three of them candidiasis was already evident before the administration of cisapride and one baby died of candida sepsis. In the remaining three infants cholestasis disappeared (in one while cisapride was continued) and subsequent liver tests yielded normal values. None of the infants in our study group showed clinical evidence of cholestasis. Liver function tests both at the beginning and the end of the study were normal.

We closely monitored all the babies during the study for cardiac rhythm disturbances. None of our infants in the cisapride group had sinus tachycardia. Several cases of prolonged QT interval syndrome due to cisapride have been reported.[21–23] The dose of cisapride used in our study (0.8 mg/kg/day) was less than that (1–1.5 mg/kg/day) used in these case reports. We recorded ECGs at the beginning and end of the study. QTc intervals were measured and were normal in both groups. Whether more frequent ECG recording or Holter monitoring of our babies could have detected transient changes in QT interval or other rhythm disturbances remains uncertain.

One could argue that larger doses than that used in this study could improve feed intolerance. However, it may not be justified in view of the increased risk of arrhythmias with larger doses. Lupoglazoff *et al*[22] reported prolonged QT interval in preterm and term infants treated with cisapride at doses of 1–1.7 mg/kg/day. They showed that the QT interval returned to normal after reducing the dose to 0.8 mg/kg/day, as used in our trial.

Based on these findings, the routine use of cisapride in preterm infants to decrease the time to establish enteral feeds or the requirement for total parenteral nutrition cannot be recommended. It may, however, be appropriate if the infant has clinically significant gastric stasis and regurgitation. Such babies should be closely monitored for cardiac rhythm disturbances until a safe dose is documented in further studies.

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