Randomised controlled trial of cisapride in preterm infants

R J McClure, J H Kristensen, A Grauaug

Abstract

Aim—To determine the effect of cisapride on gastrointestinal motility in preterm infants.

Methods—Cisapride (0.2 mg/kg, 8 hourly) or placebo was given for seven days in a double blind randomised crossover study of 10 preterm infants. Gastrointestinal motility was assessed on day 3 of each treatment. The half gastric emptying time (GET½) was determined by using ultrasonography to measure the decrease in the gastric antral cross sectional area after a feed. The whole gastrointestinal transit time (WGTT) was assessed by timing the transit of carmine red through the gut. Treatments were compared using the Wilcoxon matched pairs signed ranks test.

Results—Median (range) birthweight was 1200 (620, 1450) g and postconceptional age 33 (29, 34) weeks at recruitment. GET½ was significantly longer during cisapride treatment than during placebo; the median of the differences (95% confidence interval) was 19.2 (11, 30 minutes, p=0.008). WGTT was also longer during cisapride treatment, but the difference was not significant; the median of the differences was 11 (−18, 52 hours, p=0.1).

Conclusions—Cisapride delays gastric emptying and may delay WGTT in preterm infants. Its use to promote gastrointestinal motility in this group cannot be recommended.

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Keywords: cisapride; gastric emptying; gastrointestinal transit; gastrointestinal motility

Cisapride is a prokinetic agent and stimulates gastrointestinal motility. It is chemically related to metoclopramide, but is largely devoid of central depressant or anti-dopaminergic effects. In adults and children cisapride can increase lower oesophageal sphincter pressure and oesophageal motility, hasten gastric emptying, and accelerate small intestinal and colonic transit of luminal contents in both healthy people and patients with gastro-oesophageal reflux.1–4 It can also improve coordination of gastric, pyloric, and duodenal motor activity.5–7

Cisapride is being increasingly used in preterm infants for the treatment of gastro-oesophageal reflux, apnoea of prematurity resistant to methylxanthines, where silent gastro-oesophageal reflux is a possibility, and for poor feed tolerance due to gastroparesis or impaired intestinal motility. Cisapride is effective in improving gastro-oesophageal reflux in infants.8–10 However, we are aware of no randomised controlled study that has objectively examined the effect of cisapride on gastric emptying or intestinal motility in preterm infants. This is despite the known immaturity of gastrointestinal motor activity in this patient group.11–12

This study aimed to determine whether cisapride accelerates gastric emptying and whole gastrointestinal transit time (WGTT) in preterm infants.

Methods

The study was of a double blind, randomised crossover design. Consecutive very preterm infants (less than 32 weeks of gestation) admitted to the neonatal unit at King Edward Memorial Hospital, Perth, Western Australia, where a clinical decision was made to treat with cisapride, were eligible for the study. Cisapride was prescribed for clinically diagnosed gastro-oesophageal reflux or poor feed tolerance, defined for the purpose of this study as a total gastric aspirate volume of at least half of enteral intake over 24 hours. Infants were excluded from the study if they had a congenital anatomical gut malformation or were receiving other drugs known to substantially affect gastrointestinal motility. Treatment with caffeine was not an exclusion criterion as its use was routine to prevent apnoea.

Using previous data on gastric emptying and WGTT,11–16 a power calculation (type I error 5%, type II error 20%) established that 10 infants should be studied to detect a 25% difference in both measured outcomes of gastrointestinal motility.

On recruitment, infants were allocated according to a predetermined list of random numbers by the hospital pharmacy department to receive either seven days of cisapride treatment of 0.6 mg/kg/day in three divided doses given orally followed by seven days of a placebo (hydroxy propyl-methyl cellulose) of equivalent volume, or vice versa. The hospital pharmacy supplied cisapride and placebo preparations of identical appearance and the investigators and staff were blind to infant allocation until after the study was complete.

Gastric emptying and WGTT were measured on the third day of each treatment. Gastric emptying was assessed ultrasonically by serially measuring the change in the gastric antral cross sectional area (ACSA) following a feed, using a previously described method.13 ACSA was measured by obtaining real time ultrasound cross sectional images of the gastric antrum with the infant lying in the right lateral...
position. Vertebral bodies, the aorta, and the superior mesenteric artery were used as constant landmarks to ensure the same cross sectional plane of the gastric antrum was measured on each occasion. Images were obtained using a Diosonics Ultrasound Imaging System with a 7.5 MHz probe. Software available on the machine allowed images to be frozen on the screen, the gastric antrum cross sectional circumference to be marked with a steerable cursor, and the ACSA to be calculated.

Before each study the stomach was aspirated using a nasogastric feeding tube. The ACSA was measured before the test feed. A bolus feed of expressed breast milk or preterm formula (S26 low birthweight formula, Wyeth), depending on maternal choice, was given over 10 minutes. Immediately the feed was completed the ACSA was remeasured. The ACSA was subsequently measured at 10 minute intervals until 30 minutes had elapsed, and then continued at 15 minute intervals until 2 hours after the feed, or the prefeed value was reached. At the second measurement each baby received the same volume and type of milk feed as had been received during the first. Treatments were compared by calculating the half gastric emptying time (GET½), defined as the time taken for the ACSA to decrease by half of the maximum change seen during gastric filling.

WGTT was measured by timing the transit of the marker carmine red through the gastrointestinal tract. Carmine red (125 mg) was given via a nasogastric feeding tube over 1 minute and the time recorded. At each subsequent nappy change any faeces were inspected for evidence of the dye. WGTT was defined as the elapsed time between carmine red administration and its first appearance in the faeces. To minimise any effect of circadian rhythm, carmine red was always given immediately after a feed as near to 1500 hours as possible. Nappy changes were at the discretion of the attending nurse but were generally 3 to 4 hourly.

Statistical analysis was performed using the Wilcoxon Signed Rank test for paired non-normally distributed data. Informed parental consent was obtained before each study. The study was approved by the local research ethics committee.

Results
All 10 infants completed the study without any apparent adverse effects. Four infants were prescribed cisapride for gastro-oesophageal reflux and six for poor milk tolerance. Four infants were randomly allocated to receive cisapride first, letter A indicates that infant was randomly allocated to receive cisapride first, letter B indicates placebo.

Discussion
Mature gastrointestinal motility depends on a complex interaction of neural and hormonal control mechanisms. This is altered by external factors such as enteral feeding and illness. In preterm infants motility is also affected by gastrointestinal immaturity. The upper gastrointestinal tract displays two different functional states: the interdigestive or fasting state, and the fed or postprandial state. The fasting state is characterised by a propagative cyclical motor pattern, the migrating motor complex (MMC). The MMC is absent before 27 weeks after which it steadily develops, with mature patterns appearing only between 34 weeks and term. Not surprisingly, both gastric emptying and whole intestinal transit have been shown to be delayed in preterm infants.

In view of the immaturity of gastrointestinal motility in preterm infants it was not unexpected that, unlike in infants and adults, no acceleration of gastric emptying and intestinal transit was seen. However, it was surprising to find that cisapride actually retarded gastric emptying. The finding that in seven infants intestinal transit was slower during cisapride treatment, suggests that it may also be delayed.

Only one previous published study by Melis and Janssens was identified as having examined the effect of cisapride on gastric emptying in preterm infants. In 20 preterm infants (26 to 34 weeks of gestation) gastric emptying was
The findings of this study suggest that the use of cisapride cannot be recommended for treatment of gastric stasis or poor intestinal motility in premature infants. These effects also suggest that cisapride may worsen gastro-oesophageal reflux in this population. Until the efficacy of cisapride to treat gastro-oesophageal reflux is determined we believe that this study supports the recent statement made by the United Kingdom Committee on the Safety of Medicines and the Medicines Control Agency: “cisapride is specifically contraindicated in preterm infants.”

Editor's note: The Medicines Control Agency has stated that cisapride is contraindicated in neonates born before 36 weeks of gestation until they are 3 months of age. This is in addition to the already existing recommendation not to use it in children under the age of 12 years, although the drug is widely used in this age group.


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