Cisapride Decreases Gastroesophageal Reflux in Preterm Infants

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ABSTRACT. *Objective.* **Gastrointestinal prokinetic agents, such as cisapride, are commonly used in pediatric practice to improve gastric emptying, to decrease emesis, to improve lower esophageal sphincter tone, and to improve irritability and feeding aversion associated with gastroesophageal reflux (GER). Although cisapride seems to be effective in infants from 2 months to 14 years old, data for younger and preterm infants are not available. Whether reflux is a significant cause of reflex apnea or feeding intolerance in the preterm infant is controversial. The objective of this 1-year prospective study, started in 1998, was to determine the efficacy of cisapride for treatment of reflux and reflux-associated apnea (RAAP) in preterm infants. Before this study, the diagnosis of reflux was often made clinically and the effect of therapy on reflux or the decision to increase the dose of cisapride was made empirically. The clinical bias was that persistent apnea, not responding to caffeine, was caused by GER. We reasoned that a systematic approach to the diagnosis and treatment of reflux would improve the care of preterm infants and reduce the risk of toxicity, especially if an increased dose of cisapride showed no improvement in reflux or apnea.**

Study Design. **Twenty-four preterm infants (24–36 weeks' gestational age) had clinical apnea/pH studies when they were referred by the attending neonatologist for suspected GER. These infants were born at 28.8 ± 3.1 weeks with birth weight of 1169 ± 387 g (range: 631-2263 g). Each infant was studied before and 8 days after starting cisapride treatment. Cisapride dose was 0.09 to 0.25 mg/kg every 6 hours enterally. Treatment decisions regarding dose of cisapride were the responsibility of the attending neonatologist. The pH was recorded continuously for 24 hours at 0.25 Hz and was analyzed using EsopHogram software. A single sensor pH catheter was inserted to ~2 cm above the esophageal gastric junction. GER was defined as a drop in esophageal pH below 4.0 for a least 5 seconds, or pathologic GER was defined as a reflux index (RI) >2 standard deviation (SD) from the mean based on published norms for term infants. The following parameters were calculated from the pH recording: number of reflux events per 24 hours, duration of the longest episode, number of episodes >5 minutes per 24 hours, and RI, ie, percentage of time with pH <4.0. Each study had a combined time-lapse video recording and multichannel digital recording. Recorded parameters were: continuous pulse oximetry, electrocardiogram, respiratory effort (piezo sensor), and airflow (temperature sensor at nostrils and mouth). The recording was scored for central apneas of 10 to 14 seconds and ≥15 seconds (prolonged) and ≥10 seconds for obstructive and mixed apneas. RAAP was scored when an apnea (irrespective of the type) occurred within 1 minute of a GER event. Baseline, after cisapride, and follow-up electrocardiograms were performed because of concern about prolonged QTc and cardiac arrhythmias. The infants were 35.6 ± 4.5 weeks postconceptional age when first studied. Twelve infants (mean birth weight: 1821 ± 749 g; gestational age: 32 ± 2 weeks; postconceptional age: 35.6 ± 2.6 weeks) were identified retrospectively as controls because their baseline GER parameters were within the normal range using Vandenplas' criteria.**

Results. **Overall, cisapride treatment significantly improved the RI from 16.6 ± 15.2 to 9.1 ± 8.4 SD. The number of reflux episodes ≥5 minutes was reduced from 7.1 ± 5.8 to 4.3 ± 4.4 SD. No significant effect was seen on the total number of refluxes (/24 hours). Eight infants (33%) had no decrease in the RI after a week of treatment. Three of these infants improved after cisapride dose was increased from 0.09 to 0.25 mg/kg/dose every 6 hours. Although 0.09 mg/kg/day is the minimum effective dose, 67% of our infants did respond to this low dose. Cisapride was discontinued in 3 infants because of prolonged QTc ≥0.450 seconds (0.473 in 1 and 0.470 in 2). More data about the effect of cisapride on QTc interval are reported in *Pediatrics* in a separate article. Only 1 infant showed no improvement with increased dose. Caffeine treatment had no effect on the baseline or follow-up GER values. Although apnea indexes for central and obstructive apnea were similar before and after cisapride, mixed apnea was less during treatment. There was a significant decrease (0.32 ± 0.40 to 0.12 ± 0.17/hour) in RAAP when the one infant who had increased reflux on increased dose of cisapride was excluded as an outlier. The statistical difference, before and after cisapride, for the group is significant with the outlier omitted. The clinical significance is unclear because ~50% of the infants had minimal changes in their apnea indexes. Furthermore, ~40% of infants did not have RAAP. Although there was a significant reduction in reflux after cisapride treatment in the symptomatic infant group, reflux parameters did not normalize compared with the values of the control infants or the published norms for term infants. Five infants had RIs <2 SD of Vandenplas' normative values (<3.2%).**

Conclusion. **A low dose of cisapride was effective in decreasing, but not normalizing, the RI in the majority of the preterm infants. Our data extend the findings of Vanderplas and colleagues who found that cisapride decreases prolonged episodes of reflux in term infants (2–4 months old). Although mixed apnea was significantly decreased and there was decreased RAAP after cisapride treatment, there are insufficient data in this study to**

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claim that the treatment of reflux will significantly decrease apnea severity or improve the management of preterm infants with persistent apnea. Cisapride has been withdrawn because of concern about the risk of cardiac toxicity. If an isoform of cisapride becomes available, which theoretically has no adverse effects on cardiac conduction, randomized, controlled clinical studies should be performed to establish safety and efficacy for the management of reflux, feeding intolerance, and apnea in the preterm infant. *Pediatrics* 2001;107(4). URL: http://www.pediatrics.org/cgi/content/full/107/4/e58; *cisapride, preterm infant, reflux, apnea.*

ABBREVIATIONS. RAAP, reflux-associated apnea; GER, gastroesophageal reflux; RI, reflux index; GA, gestational age; ECG, electrocardiogram; PCA, postconceptional age; ApC, central apnea; ApO, obstructive apnea; ApM, mixed apnea; SD, standard deviation; LES, lower espohageal sphincter.

In preterm infants, gastroesophageal immaturity and reflux of gastric contents into the esophagus may be associated with reflux-associated apnea (RAAP), significant bradycardia and oxygen desaturation, inability to advance feeding volumes, irritability, and exacerbation of chronic lung disease when there is aspiration of gastric material into the lungs.

There are minimal data regarding what are normative gastroesophageal reflux (GER) parameters in preterm infants. Earlier studies suggest that the norm is the same as for term infants, such as the study by Ng and Quak,[1] or slightly less, as indicated by Jeffery and Page.[2] The relationship between reflux and apnea in infants is not yet fully understood.[3–6] Nevertheless, there is a very sensitive laryngeal vagal reflex in preterm and term infants and in newborn animals.[7,8]

Oral gastrointestinal prokinetic agents, such as cisapride, are commonly prescribed to improve gastric emptying and to treat the suspected symptomatology associated with GER. In our neonatology practice, continuous 24-hour esophageal pH recordings are obtained in infants suspected to have reflux to make the diagnosis of symptomatic GER, which is defined as a reflux index (RI) >2 SD from the mean based on published norms for term infants (see Table 1).[9] A follow-up recording was performed for this study to assess the effectiveness of treatment.

Cisapride decreases GER by enhancing the release of acetylcholine at the mesenteric plexus. In vitro studies show that it is also a serotonin (5 HT) 4-receptor agonist. This agonist action may increase gastrointestinal motility. Metabolism of cisapride is through the cytochrome P450 system, which may be immature in the preterm infant. This immaturity of the cytochrome P450 system has been hypothesized to decrease drug clearance and, thereby, to cause increased levels and toxicity.[10]

TABLE 1. Normal Ranges for GER in Infants 0 to 15 Months Old (Vandenplas and Sacre-Smits[9])

Reflux Parameter	Normal Value (Mean)	1 SD	2 SD
Number (/24 h)	7.73	14.24	20.75
Duration of longest (min)	3.83	5.75	7.67
Number >5-min duration (/24 h)	0.64	1.12	1.66
RI (%)	1.2	2.11	3.02

Cisapride had been an accepted practice for the treatment of GER in adults[11–14] and children 2 months to 14 years old.[15–18] However, the drug was withdrawn by the Food and Drug Administration and the manufacturer in mid-July 2000, because of concerns about risk for lethal cardiac arrhythmias and, thus, no longer will be available for clinical use in the United States. Nevertheless, there were minimal data about its antireflux efficacy and effect on apnea management in preterm infants and newborns.

McClure et al[19] raised a concern about the efficacy of cisapride when they observed that there was a delay in gastric emptying in preterm infants who received cisapride. From this study, the authors concluded that cisapride should not be used in preterm infants because it could exacerbate feeding problems and reflux. Additionally, there is a concern about the possible greater toxicity in this preterm population for prolonged QTc interval.[20,21]

The purpose of this prospective study, started in 1998, was to determine the efficacy of cisapride for the management of GER and RAAP in preterm infants. Before this study, the diagnosis of reflux was often made clinically and the effect of therapy on reflux or the decision to increase the dose was made empirically. We reasoned that a systematic approach to the diagnosis and treatment of reflux would improve care of the preterm infant and reduce the risk of toxicity, especially if an increased dose showed no improvement in reflux or apnea.

METHODS

This study was approved by the Stanford University Panel on Human Subjects in Medical Research.

Infants Symptomatic for Reflux

Twenty-four preterm infants (24–36 weeks' gestational age [GA]) hospitalized at Lucile Salter Packard Children's Hospital at Stanford were referred to the Pediatric Pulmonary Laboratory for apnea/pH recordings. These studies were ordered by the attending neonatologist when reflux apnea was suspected and/or for feeding intolerance, ie, significant gastric residuals or regurgitation after feeding. A repeat apnea/pH study was performed within 8 days of cisapride. The initial cisapride dose was 0.09 to 0.10 mg/kg/dose orally every 6 hours. Treatment decisions were the responsibility of the attending neonatologist.

Baseline, after cisapride, and follow-up electrocardiograms (ECGs) were required because of concern about the risk for prolonged QTc and cardiac arrhythmias. Cisapride was contraindicated if QTc was ≥0.450 seconds or if there was congenital heart disease or family history of long QTc. A pediatric cardiologist read the QT intervals.

Selected clinical information is presented in Table 2.

Improvement of GER was assessed by a decrease in the RI. If no improvement was seen, cisapride dose was increased to a maximum dose of 0.25 mg/kg/dose 4 times daily and a repeat study was performed.

Control Infants

Infants who had a negative baseline pH study by Vandenplas' criteria[9] (Table 1) were retrospectively identified as control infants. Six infants were female and 6 were male. Mean birth weight was 1821 ± 749 g (1002–3124 g); GA, 32 ± 2 weeks (26–36 weeks); and postconceptional age (PCA), 35.6 ± 2.6 weeks (31.9–41 weeks).

TABLE 2. Clinical Data of Infants With Symptomatic GER

	Sex	GA (Weeks)	PCA† (Weeks)	PCA ‡ (Weeks)	BW (g)	Pre S	Post S	C†	C‡	O_2†	O_2‡
1	M	24	35	36	763	Yes	Yes	—	—	No	No
2	M	27	31	32	900	Yes	No	19	16	No	No
3*	M	29	35	36	1376	Yes	No	—	—	Yes	Yes
4*	M	36	47	48	980	No	Yes	—	—	Yes	Yes
5	M	27	34	35	957	Yes	No	15	—	Yes	Yes
6	F	28	30	31	1261	Yes	No	16	15	Yes	No
7	F	30	32	33	1381	Yes	No	—	—	No	No
8	F	26	37	38	891	Yes	No	—	—	Yes	Yes
9	M	31	35	36	1259	Yes	No	14	—	No	No
10	M	28	39	40	1253	Yes	No	—	—	Yes	Yes
11*	F	26	37	38	803	Yes	No	—	—	Yes	Yes
12	F	34	36	37	2263	No	No	15	—	No	No
13	F	28	30	31	899	Yes	No	13	18	No	No
14*	M	32	36	37	1741	No	No	—	—	No	No
15	M	32	36	37	1600	No	No	—	—	No	No
16	M	25	36	37	1086	Yes	Yes	—	—	Yes	Yes
17	M	28	33	34	946	Yes	Yes	27	15	Yes	Yes
18	M	28	31	32	872	Yes	Yes	17	13	Yes	Yes
19*	F	32	34	35	1412	Yes	Yes	9	20	Yes	Yes
20	F	30	31	32	1400	Yes	No	21	12	No	No
21*	M	25	42	43	631	Yes	Yes	—	—	Yes	Yes
22	M	32	33	34	1665	Yes	No	12	18	No	No
23	M	25	47	48	822	Yes	Yes	—	—	No	No
24*	M	28	35	36	884	Yes	No	22	23	Yes	Yes

Pre S indicates prenatal steroids; post S, postnatal steroids; —, no caffeine; C, caffeine level (μg/mL); O_2, nasal oxygen; BW, birth weight; M, male; F, female.
* Infants who had no decrease in RI after cisapride (see also Tables 4 and 5).
† Baseline study.
‡ ≥48 hours after cisapride.

Protocol for the Apnea/pH Study

The overnight apnea portion of the apnea/pH study was obtained over a period of 15 to 16 hours. Each study had a combined time-lapse video recording and a multichannel digital recording (Embla, Flaga hf, Reykjavik, Iceland). Recorded parameters were: continuous pulse oximetry (Nonin Medical, Plymouth, MN; Embla, Flaga hf), ECG, respiratory effort (Piezo Sensor, ProTech, Woodinville, WA) and airflow measured with a temperature sensor at the nostrils and mouth (BreathSensor, Mallinckrodt Inc, Minneapolis, MN). The recording was scored for: central apnea (ApC), obstructive apnea (ApO), mixed apnea (ApM), periodic breathing, oxygen desaturation, and bradycardia. Apnea episodes were scored as ApC when there was an absence of both respiratory effort and airflow. Short ApC episodes were defined as lasting 10 to 14 seconds and prolonged episodes were >15 seconds. ApO was defined as presence of respiratory effort and absence of airflow for 10 seconds or longer. ApM was defined as presence of at least 3 seconds of ApC with an additional component of ApO totaling 10 or more seconds. Apnea index was computed as the number of apneas/hour. Observers trained in apnea scoring made the final determination of events by visually reviewing and scoring the recording.

A single sensor pH catheter (Zinetics 24 ME, Medtronic Functional Diagnostics Inc, Copenhagen, Denmark; monocrystalline antimony was calibrated using standard buffer solutions of pH = 1.07 and 7.01. Infants fasted for at least 2 hours before the test to avoid emesis when the pH probe was inserted. Insertion length was calculated for each individual infant to position the probe ~2 cm above the esophageal gastric junction using the following formula: (length of infant (cm)/4) + 2 cm.[22] The pH probe was lubricated with sterile water and inserted nasally. The probe was advanced into the stomach to verify that the gastric pH was <2. The probe was then positioned at the calculated length and secured to the cheek and behind the ear with tape. A chest radiograph was obtained to check the calculated position when the gastric pH was >2. The pH was recorded (Digitrapper, Medtronic Functional Diagnostics Inc) continuously for 24 hours at 0.25-Hz and analyzed using *EsopHogram Software, Version 5.7* (Medtronic Functional Diagnostics Inc). The apnea and the time-lapse video recording were synchronized with the pH recording. GER was defined as a drop in esophageal pH below 4.0 for at least 5 seconds. The following parameters were calculated for the pH recording: number of reflux events per 24 hours, duration of the longest episode, number of episodes >5 minutes per 24 hours, and RI (percentage of time with pH <4.0). RAAP, ie, reflex apnea, was scored when an apnea (irrespective of the type) occurred within 1 minute of a GER event.

Statistical Analysis

StatView, Version 5.0 (SAS Institute Inc, Cary, NC) was used for statistical analysis. Nonparametric (Wilcoxon signed rank) tests were used because the data were not normally distributed.

RESULTS

Infants Treated With Cisapride

Twenty-nine preterm infants admitted from November 1998 through October 1999 were recorded because of clinically suspected reflux. The clinical decision to treat with cisapride was based on abnormal pH results (RI >2 SD from control; see Table 1). Cisapride dose was 0.09 to 0.25 mg/kg/dose every 6 hours. In total, 9 infants were started at 0.09 mg/kg/dose 4 times daily and 6 infants (66%) showed decreased GER with this dose. Mean cisapride dose was 0.10 ± 0.02 mg/kg/dose every 6 hours. Sixteen of the infants (67%) were male. Mean GA was 28.8 ± 3.1 weeks and mean birth weight was 1169 ± 387 g (631–2263 g). Mean PCA at the first (baseline) study was 35.6 ± 4 weeks. Mean PCA at the second (after cisapride) study was 36.5 ± 4 weeks. Eight infants (33%) had a history of suspected necrotizing enterocolitis, ie, abdominal distention and abnormalities on abdominal radiograph suggesting intramural air without perforation or an abnormal intestinal gas pattern that resolved with medical management. Seven infants (29%) had a history of patent ductus

arteriosus. Six received indomethacine therapy and none had surgery. Two infants (8%) had intracranial hemorrhage (grade I; $n = 1$; grade II; $n = 1$). One infant was diagnosed with vertebral, anorectal, tracheal, esophageal, and renal malformations syndrome. Twelve infants (48%) were on caffeine treatment during the baseline study and 9 infants (36%) during the after cisapride study. Thirteen infants (54%) had nasal oxygen supplementation during the baseline study and 12 infants (50%) during the after cisapride study (see Table 2). Five infants were excluded, 4 because their after cisapride study was not performed within 8 days after cisapride; and the fifth infant previously had surgery for necrotizing enterocolitis with a perforation and initially did well on cisapride but later developed distal intestinal obstructions and required another surgery.

Effects of Cisapride on Different Reflux Parameters

Cisapride treatment, in symptomatic infants as a group, significantly reduced the RI (Table 3; Fig 1; Wilcoxon signed rank test, $P = .017$). The number of episodes ≥5 minutes (24 hours) was also significantly reduced ($P = .026$). No significant effect was seen on the total number of refluxes (/24 hours) or duration of the longest episode.

Eight infants (33%) showed no decrease in RI after a week on cisapride therapy (Fig 1; Table 4). Three of these infants improved after cisapride dose was increased from 0.09 to 0.25 mg/kg/dose every 6 hours (Table 5). Cisapride was discontinued in 3 infants because of prolonged QTc. Three infants had no follow-up. Only 1 infant (infant 19; Table 5) showed no improvement with increased dose.

Medical Status and Cisapride Treatment Outcome

There was no association between prenatal or postnatal steroids, suspected necrotizing enterocolitis, patent ductus arteriosus, or intracranial hemorrhage and the apnea index or RI. However, a greater reduction in RI was seen in infants who received prenatal steroids (Δ RI = 9.9 ± 17.8 vs Δ RI = 1.2 ± 4.5; $P = .08$). Caffeine treatment had no effect on the baseline or follow-up GER values. There was no relationship between PCA and the response to cisapride treatment (the highest correlation, r^2 value ≤0.292).

Cisapride and Apnea

The amount of RAAP or the amount of ApC and ApO were not significantly improved with cisapride (Table 6). However, ApM was significantly decreased ($P = .026$). Figure 2 shows the individual

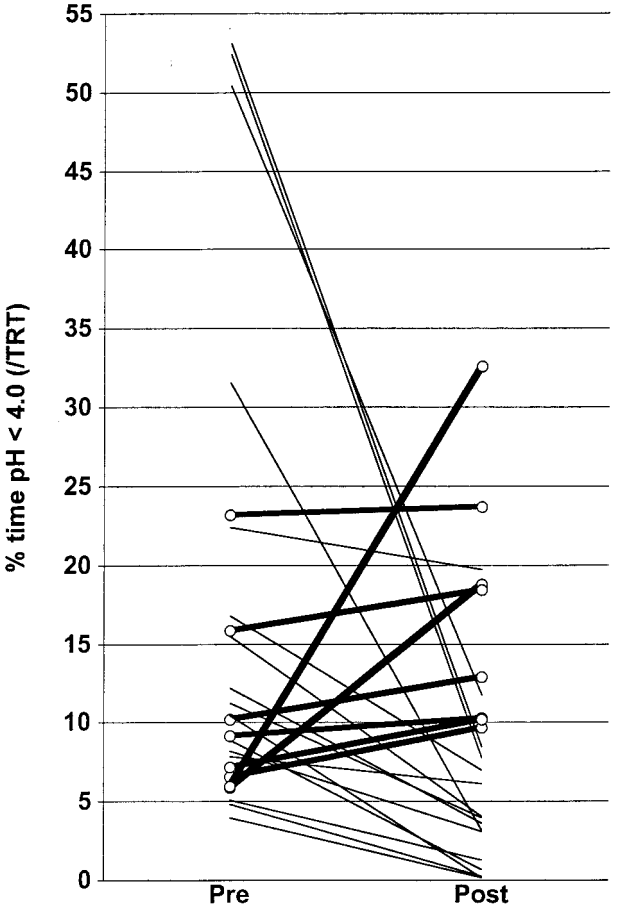

Fig 1. Individual before and after cisapride RIs (percentage of time pH: <4.0). Cisapride treatment in symptomatic infants as a group significantly reduced the RI; however, 8 infants (bold lines) showed no decrease in RI after a week on cisapride therapy.

before and after cisapride RAAP indexes that decreased in all but 5 of the infants. One had an unusually large increase. If the data from this outlier infant (infant 19; see Tables 4 and 5), who had a marked increase in reflux (RI: 21.4–36.2) on increased dose of cisapride, was excluded, the effect of cisapride on RAAP was significant ($P = .034$). Sixty-two percent of the infants had RAAP. Seven of the 14 who had RAAP before and after cisapride had <5 events for the entire study.

Despite significant reduction in reflux after cisapride treatment in symptomatic infants, reflux parameters did not normalize compared with the values of the control infants (Table 7). However, 5 infants had RI within 2 SD of Vandenplas' normative values.

TABLE 3. *P* Values and Reflux Parameters Before and After Cisapride for All 24 Symptomatic Infants

Reflux Parameter	Before Cisapride	After Cisapride	*P* Value
Number (/24 h)	91.7 ± 45.3 (46–217)	73.4 ± 65.3 (2–260)	.068
Duration of longest (min)	39.5 ± 41.2 (4–178)	23.8 ± 23.1 (1–77)	.11
Number >5-min duration (/24 h)	7.1 ± 5.8 (0–25)	4.3 ± 4.4 (0–17)	.026
RI (%)	16.6 ± 15.2 (4–53.1)	9.1 ± 8.4 (0.2–24)	.017

Mean, SD (range) are given. After cisapride values were measured within 1 week after cisapride therapy.

TABLE 4. Differences Were Calculated for After Cisapride Minus Baseline Reflux Parameters for Eight Infants Who Did Not Improve With Cisapride

	Number/ 24 Hours	Duration of Longest (Minutes)	Number ≥5 Minutes	RI (%)
4	22	−15	−2	1.1
14	8	6	2	3.1
3	−39	5	2	3.0
19	94	43	8	12.9
24	43	39	−5	0.5
21	135	17	48	26.6
17	−47	67	0	2.7
11	−58	22	5	2.6

Difference = after cisapride minus baseline. Increase or decrease in each parameter is presented by positive or negative values, respectively.

DISCUSSION

In the present study, infants who had reflux values >2 SD for term infant norms were diagnosed as symptomatic for GER.[9] There are no data to indicate that pH reflux parameter norms are very different in preterm than in term infants.[1,2] We found that cisapride was effective in reducing GER in the majority of these preterm infants. Initially, 16/24 infants improved, and after cisapride dose was increased from 0.09 to 0.25, another 3 infants (19/24) improved. Because cisapride blood levels were not obtained, the basis for the differences in response is not clear. One explanation could be differences in the level of cisapride metabolism. In the early neonatal period, a delayed maturation of the major cytochrome P450 isoforms expressed in the liver and intestine, which are important for the metabolism of cisapride, has been reported recently.[23,24]

We did find a trend toward reduced RAAP on cisapride therapy. One infant, after cisapride, had an increase of RAAP from 3 to 29 and an increase in RI from 5.9 to 18.8 and was considered an outlier (Fig 2). Excluding that infant's values resulted in a significant ($P = .034$) decrease of RAAP in the rest of the population from 0.32 ± 0.40 to 0.12 ± 0.17 (/hour). Although the difference before and after cisapride for the group is significant, with the outlier omitted, it is still not significant clinically because ~50% had minimal changes. Furthermore, ~40% of infants did not have RAAP at all. Although ApM was significantly decreased after cisapride treatment and there was decreased RAAP, there are insufficient data in this study to claim that the treatment of reflux will significantly decrease or improve the management of preterm infants with persistent apnea. There was no effect of caffeine treatment on the efficacy of cisapride to reduce RI, which corroborates the recent report of Kentrup et al[25] who found similar amount of improvement in pH recorded reflux events in a group of preterm infants on caffeine for apnea management.

Eight infants did not respond to initial cisapride treatment. We do not have a clear explanation why these infants did not respond (see Table 5). One explanation might be in the inter individual differences in cisapride metabolism. We were not able to monitor serum levels of cisapride to establish such differences. Three of these infants (Table 5) received a cisapride dose of 0.09 mg/kg/dose every 6 hours. They showed improvement after cisapride dose was increased from 0.09 to 0.25 mg/kg/dose every 6 hours. Although 0.09 mg/kg/day is the minimum effective dose, 67% of our infants did respond to this low dose. A double-blind placebo control treatment trial and drug levels would be the preferred design for additional study of reflux treatment.

Continuous 24-hour measurement of esophageal pH is generally accepted as a reliable method for the quantification of GER. Ideally, pH measurements with a double sensor (esophageal and gastric pH) instead of a single sensor pH catheter may provide more information about reflux. Washington et al[26] showed that the use of a single sensor pH catheter underestimates the occurrence of refluxes. We believe our measurements are accurate for the technique used and comparable to the norms of Vandenplas et al,[9] which are based on the same method. We did not measure whether feeding tolerance improved. Enriquez et al[27] showed in a randomized,

TABLE 5. Follow-Up of Preterm Infants Who Did Not Initially Improve on Cisapride Treatment

	RI Baseline	RI After Cisapride	RI Follow-Up 1	RI Follow-Up 2	Dose Initial (Final)	Comments
4	9.2	10.3	1.8	—	0.09 (0.2)	Increased dose improved RI.
14	6.6 QTc = 0.417 s	9.7 QTc = 0.470 s	—	—	0.1 (0)	Prolonged QTc interval, cisapride discontinued.
3	7.2	10.2	—	—	0.1	No follow-up.
19	5.9	18.8	21.4	36.2	0.09 (0.2)	Increased dose did not improve RI (follow-up 1). Cisapride discontinued. Reglan started. Follow-up 2 showed no improvement on Reglan.
24	23.2	23.7	2.5	—	0.1 (0.2)	Increased dose improved RI. Discharged on cisapride.
21	6.0	32.6	—	—	0.1	No follow-up.
17	10.2 QTc = 0.395 s	12.9 QTc = 0.470 s	6.5	18.4	0.09 (0.25)	Increased dose improved RI (follow-up 1). Prolonged QTc interval, cisapride discontinued. Reglan started. Follow-up 2 showed no improvement on Reglan.
11	15.8 QTc = 0.410 s	18.4 QTc = 0.473 s	12.1	—	0.1 (0)	Prolonged QTc interval, cisapride discontinued. Started on Reglan.

Dose indicates cisapride dose (mg/kg/dose 4 times daily).

TABLE 6. Apnea Indexes Before and After Cisapride in 24 Symptomatic Preterm Infants

Apnea Type	Apnea Index, Before Cisapride	Apnea Index, After Cisapride	*P* Value
ApC <15 s	0.62 ± 0.89	0.54 ± 0.68	.4
ApC ≥15 s	0.36 ± 0.70	0.41 ± 0.89	.3
ApO ≥10 s	0.09 ± 0.15	0.04 ± 0.14	.2
ApM ≥10 s	0.5 ± 0.47	0.3 ± 0.36	.026
RAAP	0.3 ± 0.38	0.2 ± 0.39	.12

Mean and SD are given.

TABLE 7. Reflux Parameters in the Control (n = 12) and Symptomatic Infants Who Responded to Cisapride (n = 16)

Reflux Parameter	Control Infants	Before Cisapride	After Cisapride
Number (/24 h)	6.5 ± 5.7	83 ± 37.1	79.5 ± 70.9
Duration of longest (min)	1.7 ± 1.3	51.4 ± 46.9	24.2 ± 22.7
Number >5-min duration (/24 h)	0 ± 0	8.9 ± 7.1	5.2 ± 6.1
RI (%)	0.4 ± 0.4	19.7 ± 17.5	10.2 ± 10.1

double-blind, placebo study that feeding tolerance did not significantly improve with cisapride in 34 preterm infants of ≤32 weeks' GA in comparison with the placebo group. Another way to measure the efficacy of cisapride is to measure gastric emptying. McClure et al[19] showed a delay in gastric emptying with cisapride treatment and, therefore, did not recommend the use of cisapride in preterm infants. However, their number was small (n = 10) and because they did not measure esophageal pH or feeding intolerance, it remains unclear what the consequence of the gastric delay would be in relation to the presumed increase in lower esophageal sphincter pressure caused by cisapride. Endoscopic manometric measurements were not made in these infants; therefore, whether there was an effect of cisapride on the lower espohageal sphincter (LES) pressure is unknown. Omari et al[28,29] recently reported that the LES motor function is well developed in very preterm infants at 26 to 33 weeks' gestation. They proposed that the mechanism for reflux is transient relaxation of the LES.

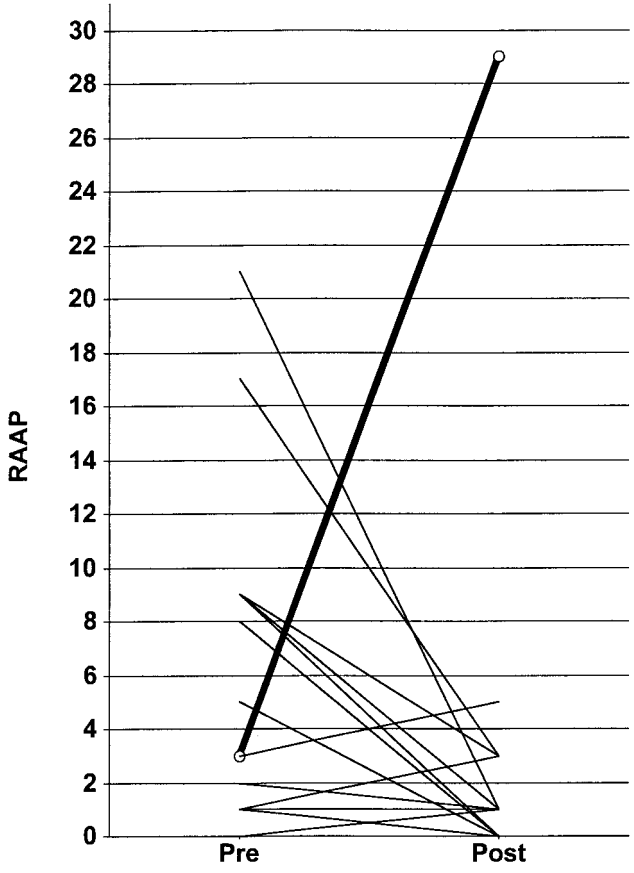

Fig 2. Individual before and after cisapride RAAP indexes. An increase was seen in 5 of the infants. One infant (bold line) had an unusually large increase. If the data from this outliner infant were to be excluded, the effect of cisapride on RAAP would be significant (P = .034).

Three infants (13%) in our study developed prolonged QTc interval (≥450 seconds). All of the infants in the study had routine continuous ECG monitoring and none of the infants treated with cisapride had arrhythmias. More data about the effect of cisapride on QTc interval are reported in a separate article.

Our data extend the findings of Vandenplas et al,[16] who found that cisapride decreases prolonged episodes of reflux in term infants (2–4 months old), to the preterm infant. Cisapride is no longer available for clinical treatment of reflux. More information about the incidence of reflux in preterm infants and whether it is a significant problem that interferes with establishing adequate enteral caloric intake or contributes to continuing apnea and oxygen desaturations needs additional study. We believe that the amount of reflux as defined in our symptomatic preterm infants is pathologic and requires intervention. It would be unwise to initiate a clinical trial without knowing the effect of the treatment on the symptom, the dose, or potential toxicity in the premature infant. Furthermore, clinical studies are needed to determine whether a drug that is effective in increasing gastrointestinal motility or in increasing esophageal sphincter pressure will indeed improve enteral caloric intake and outcome. If an isoform of cisapride becomes available, which theoretically has no adverse effects on cardiac conduction, studies to establish efficacy for the management of reflux, feeding intolerance, and apnea in the preterm infant should be initiated.

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