Effect of Cisapride on Corrected QT Interval in Neonates

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Abstract

Objective : To evaluate the effect of cisapride on corrected QT (QTc) interval in neonates at the Queen Sirikit National Institute of Child Health.

Method : A prospective study was performed to see the effects of cisapride on QTc interval in 20 neonates between 1st July 2001 and 31st January 2002. QTc interval was determined just before, 48 hours, 7 days and 15 days after the start of treatment with cisapride. QTc interval was calculated by averaging $QT/\sqrt{RR}$ values obtained from 5 consecutive beats in lead II of the EKG. Baseline electrolyte and calcium levels were drawn on all infants before treatment of cisapride. Drug dose ranged from 0.1-0.2 mg/kg every 6 to 8 hours.

Results : Twenty infants were enrolled in the survey but complete data was obtained on 18 infants only. QTc interval of > 0.45 seconds was not found in any neonate. There was no significant difference of QTc interval before and 48 hours, 7 days and 15 days after cisapride administration ($p = 0.861$). There were also no statistically significant effects of age at starting cisapride, weight, gestational age and dose on QTc interval ($p = 0.581$, 0.65, 0.8, and 0.497). There were no adverse effects such as diarrhea or jaundice during the study.

Conclusion : Term and preterm infants using cisapride at the doses of 0.4-0.8 mg/kg/day did not develop QTc prolongation, arrhythmias or adverse effects. In the absence of risk factors, cisapride may be safe for use in neonates.

Key word : Cisapride, QTc Interval, Neonates

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Gastroesophageal reflux (GER) is a condition frequently found in neonates[1,2]. It is defined as the retrograde movement of gastric contents into the esophagus and above, commonly caused by the relaxation of lower esophageal sphincter (LES)[3,4]. The LES tone is normal in most full term infants but occasionally the pressure drops, causing reflux, which is usually asymptomatic[5]. On the other hand, reflux occurs more frequently in premature neonates. This is due to LES incompetence, longer gastric emptying time and more gastrointestinal dysmotility found in premature neonates[1,4]. Gastric antral distention caused by the above stated factors cause GER feeding intolerance especially in neonates less than 32 weeks of gestational age. GER in preterm infants usually presents with symptoms such as regurgitation, vomiting after feeds, apnea and bradycardia. Some infants may even present with aspiration pneumonia, recurrent pneumonia and failure to thrive[1].

Treatment of GER depends on the severity of the disease[1,3,4]. If there is vomiting but the infant is thriving well then conservative treatment such as dietary modifications and position change during feeds may be indicated. All reflux provoking or aggravating factors are eliminated. Medical therapies include prokinetics (metoclopramide, cisapride) and acid suppression agents such as H2 blockers (ranitidine and cimetidine) and proton pump inhibitors (omeprazole)[1,4]. Cisapride, a benamide compound enhances acetylcholine release from post ganglionic nerve endings of mesenteric plexus, thereby increasing antral motility and duodenal contractility; increases coordination of antroduodenal function and accelerates gastric emptying. A number of studies have indicated that cisapride is effective for the treatment of GER and feeding intolerance in children and premature infants[6,7]. It has also been used in post-operative gastrointestinal tract ileus, esophagitis, dyspepsia and constipation in children and adults[8-12].

Unfortunately, the safety of cisapride has been questioned due to reports of cardiac arrhythmias and death associated with its use[13-17]. Risk factors associated with cardiac effects include conditions that lead to elevated drug serum levels such as high drug dose, concurrent treatment with drugs known to inhibit the cytochrome P450 system (CYP3A4) isoforms, the primary pathway for cisapride metabolism[6,13,14, 18,19]. Other risk factors include underlying cardiac disease, electrolyte disturbance, renal insufficiency and hepatic dysfunction. Premature infants and neonates are also considered a high-risk group because of reduced activity of the cytochrome P450 enzyme in this age group. Since cisapride has been used routinely in our neonatal unit, and to our knowledge there has not been any published study on the effect of cisapride in Thai children, the authors decided to conduct the present study to see its effect on neonates.

Objectives

To evaluate the effects of cisapride on corrected QT (QTc) interval in neonates.

PATIENTS AND METHOD

All neonates admitted to the neonatal unit of Queen Sirikit National Institute of Child Health (QSNICH) from 1st July 2001 to 31st January 2002 and treated with cisapride for GER were included in the present study. GER was diagnosed either by positive barium study and/or by clinical signs and symptoms of reflux including regurgitation, vomiting, apnea, bradycardia not explained by any other causes. Excluded from the present study were infants with QTc of more than 0.45 seconds before starting treatment, with congenital heart disease, or infants with a concomitant prescription of drugs known to increase QTc interval (ketoconazole, fluconazole and erythromycin). Demographic data was obtained from the patient's chart. Electrocardiograms were performed just before and 48 hours, 7 days and 15 days after initiation of cisapride treatment. EKGS were preformed using cardiofax ECG 6511 with a paper spread of 25 mm per second. QTc interval was calculated as $QT/\sqrt{RR}$ in five consecutive beats using lead II and the five values were then averaged. Each EKG was read independently by one of the investigators and by the pediatric cardiologist from our institute. A QTc interval higher than 0.45 seconds was considered prolonged.

Blood tests for potassium and calcium were performed on all infants before starting the study and at any time the QTc interval was prolonged after starting treatment. Serum potassium level of < 3.5 mmol/l and serum calcium level of < 2.1 mmol/l were regarded as abnormal.

The dosage of cisapride ranged from 0.1-0.2 mg/kg every 6 to 8 hours given at the discretion of the attending neonatologist.

Statistics

Demographic data was analyzed as median and 5-95 per cent. Each infant acted as his/her own control. Comparisons between QTc interval before

Table 1. Demographic data.

	Median (5-95%)
Birth weight (grams)	1,500 (1,000-3,900)
Gestational age (weeks)	31 (29-40)
Postnatal age at cisapride initiation (days)	39 (24-78)
Gestational age at cisapride initiation (weeks)	38 (35-45)
Weight at cisapride initiation (grams)	1,995 (1,000-4,210)

and after cisapride were performed by repeated measurement analysis of variance (ANOVA). Multivariate test was used to analyze the interaction between QTc and age at starting treatment, weight, gestation age and dosage of cisapride. P-value of less than 0.05 was considered significant.

RESULTS

A total of 20 infants were enrolled in the present study between July 2001 and January 2002. Two neonates were subsequently excluded from the study because cisapride was discontinued during the study. One neonate did not have an EKG performed before starting cisapride (0.2 mg/kg every 6 hours) but QTc followed at 48 hours and 7 days were within normal range. Barium study done on the 11th day of therapy was normal so the therapy was discontinued. The second patient had a normal QTc interval before, 48 hours and 7 days (0.42.0.42 and 0.43 seconds) after cisapride initiation but developed sepsis during the second week of treatment hence was withdrawn from the study. Of the 18 infants who completed the present study, 12 were males and 6 females. The median (5-95% range) birth weight and gestation age in the study group were 1,500 (1,000-3,900) grams and 31 (29-40) weeks respectively. The median (5-95% range) of postnatal gestational age, weight and days at initiation of cisapride were 38 (35-45) weeks, 1,995 (1,000-4,210) grams and 39 (24-78) days respectively (Table 1). The dose of cisapride ranged from 0.1-0.2 mg/kg every 6 to 8 hours. All infants had a normal serum potassium and calcium level at initiation of cisapride.

During the present study, there were three different doses of cisapride studied (Table 2). Box test for homogeneity of variance of QTc interval between the groups before, 48 hours, 7 days and 15 days after cisapride did not show any significant difference p = 0.795. Analysis by repeated measured analysis of variance also did not show any significant difference of QTc interval before and 48 hours, 7 days and 15 days after cisapride administration p = 861. As shown in Table 3, no infant had a significant prolongation (> 0.45 seconds) of QTc interval. Statistical analysis by multivariate analysis adjusted for age at initiation of cisapride, weight, gestational age and drug dose did not show any statistical difference p = 0.581, 0.65, 0.8 and 0.497. No infant had clinical deterioration, cardiac arrhythmias or any adverse effects during the course of treatment.

One neonate (number 10 in Table 3), a male with a birth weight of 1,450 grams, 31 weeks gestational age who started cisapride on the 63rd day of life at a dose of 0.2 mgs/kg every 6 hours had a QTc interval of 0.44 seconds after 48 hours. His dose was reduced to 0.1 mgs/kg every 6 hours. When followed, the QTc interval was 0.43, 0.40, 0.40 and 0.38 seconds on days 3, 6, 7 and 15.

Our 13th patient (Table 3), a 1,000 gram, 30 weeks' gestation male infant whose cisapride was started on the 99th day of life (barium proven severe GER) at a dose of 0.1 mgs/kg every 6 hours had a feed related cyanotic spell 8 days after starting cisapride. Hence cisapride was increased to a dose of 0.2 mgs/kg every 6 hours. QTc intervals followed were 0.4 and 0.36 seconds at 11 and 15 days.

DISCUSSION

Concerns regarding the safety of cisapride have arisen since many reports published have shown

Table 2. Dose of cisapride.

Dose of cisapride	Number of infants	%
0.2 mg/kg every 6 hours	11	61.1
0.2 mg/kg every 8 hours	2	11.1
0.1 mg/kg every 6 hours	5	27.8

Table 3. QTc interval.

Patient	QTc interval (second)			
	Before	48 hours	7 days	15 days
1	0.36	0.38	0.40	0.37
2	0.38	0.39	0.35	0.38
3	0.38	0.42	0.42	0.41
4	0.38	0.41	0.37	0.40
5	0.39	0.375	0.38	0.40
6	0.37	0.38	0.35	0.39
7	0.40	0.44	0.43	0.41
8	0.37	0.35	0.40	0.41
9	0.39	0.40	0.40	0.38
10	0.40	0.44	0.40	0.38
11	0.41	0.35	0.35	0.39
12	0.38	0.38	0.37	0.39
13	0.38	0.41	0.37	0.36
14	0.39	0.41	0.37	0.40
15	0.41	0.40	0.38	0.38
16	0.39	0.40	0.42	0.42
17	0.40	0.40	0.38	0.39
18	0.38	0.39	0.41	0.42

severe cardiac arrhythmias (torsades de pointes, bradycardia, prolonged QT interval) and death associated with its use[13-15,17]. However, these have occurred mainly in chronically ill patients or in patients who were simultaneously on other medications that affected the cytochrome p450 enzyme system such as macrolide antibiotics or the azole antifungals. Nonetheless, this has led to restriction of cisapride to a limited access program supervised by gastroenterologists in the United States of America and Europe[20]. The group causing most concern has been that of the neonates especially premature babies < 32 weeks of gestation in whom this drug is frequently used. The immature cytochrome P450 enzyme system causes a delay in the drug excretion and hence causes an increase in serum drug level after multiple doses[21].

Dubin et al[15] in their study of 25 preterm infants showed that 48 per cent developed repolarization abnormalities. This was similar to a study published by Bernadini et al[16] who found a significant increase in the QTc interval in 21 term infants. However, only 6 patients in this group had a QTc interval that exceeded 0.45 seconds. In both these studies there were no clinically symptomatic patients. Khongphatthanayothin et al[17] studied the effect of cisapride in children between 17 days and 12.5 years. Only 13 per cent were found to have a prolonged QTc interval of which 85 per cent had other contributing factors that resulted in prolongation of QTc interval. Cools et al [21] showed trough and anticipated peak plasma levels of cisapride/norcisapride to be significantly higher in premature compared with term infants and concluded that premature infants less than one month could be at a higher risk of side effects. They suggested a lower dose for preterm infants.

On the other hand, the present study did not show any prolongation of QTc interval when treated with cisapride at a dose not more than 0.8 mg/kg/day and even when adjusted for weight, gestation age and dose the authors did not find any significant change in the interval. This was similar to the study published by Levine et al[22], who also did not find any prolongation of the QTc interval with 0.8 mg/kg/day of cisapride in 30 infants. They also did not find any difference in the interval between term and preterm neonates. Similarly, Costalos et al[23] in their study of low dose cisapride (0.1 mg/kg every 8 hours) in 20 low birth weight infants concluded that not only does cisapride significantly shorten gastric emptying but it also reduces the QTc interval. Ward et al[24] did a survey on ~ 11,000 preterm infants less than 32 week's gestation who had been treated with cisapride, no deaths were attributed to cisapride. Three non-fatal arrhythmias were reported, two associated with a ten fold dosing error and the third case was co-

treated with erythromycin. Diarrhea was reported in 12 cases and reversible liver enzyme change in one.

The weakness of the present study probably lies in its small sample size, as a total number of 33 neonates were required when calculated using α error of 0.1 and power of 80 per cent. The authors also did not obtain the peak and trough drug levels and hence could not correlate them with the QTc interval.

In conclusion, the authors' were not able to show any prolongation of QTc interval in the group of neonates, and also did not find any correlation between QTc interval and weight, gestational age and dose of cisapride. In the absence of risk factors that alter cisapride metabolism, it may be safe to use it in neonates. However, a larger study may be needed to confirm this.

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ผลของยา cisapride ต่อ corrected QT interval ในทารกแรกเกิด

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วัตถุประสงค์ : เพื่อศึกษาผลของยา cisapride ต่อ corrected QT (QTc) interval ในทารกแรกเกิดที่ได้รับยานี้ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

วิธีการศึกษา : ทำการศึกษาแบบ prospective ในผู้ป่วยทารกแรกเกิด 20 ราย ที่ได้รับยา cisapride ในหอผู้ป่วยทารกแรกเกิด โดยทำ EKG lead II และคำนวณวัดค่า QTC interval = QT $\sqrt{RR}$ เฉลี่ย 5 ค่าก่อนให้ยาหลังเริ่มให้ยา 48 ชั่วโมง 7 วัน และ 15 วัน ตรวจ electrolyte, calcium ก่อนให้ยา cispride ขนาดยาที่ให้ 3 ขนาด คือ 0.2 มก/กก ทุก 6 ชั่วโมง, 0.2 มก/กก ทุก 8 ชั่วโมง, และ 0.1 มก/กก ทุก 6 ชั่วโมง

ผลการศึกษา : ได้ข้อมูลผู้ป่วยครบถ้วน 18 ราย จาก 20 ราย พบว่าหลังจากให้ยา cisapride ไม่มีผู้ป่วยรายใดที่ QTc interval มากกว่า 0.45 วินาที ค่า QTc ก่อนให้ยาและหลังให้ยา 48 ชั่วโมง 7 วัน และ 15 วัน ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ p = 0.764 อายุในวันเริ่มให้ยา น้ำหนัก อายุครรภ์และขนาดยาไม่มีผลต่อ QTc interval (p = 0.581, 0.65, 0.8 และ 0.497 ตามลำดับ) และไม่พบผลข้างเคียงอื่น ๆ ของยาเช่น ท้องเสีย, ตัวเหลือง

สรุป : ยา cisapride ที่ให้แก่ทารกแรกเกิดคลอดครบกำหนดและคลอดก่อนกำหนด ขนาด 0.4–0.8 มก/กก/วัน ในการศึกษาครั้งนี้ไม่พบว่ามี QTc interval ยาวขึ้น ดังนี้ถ้าไม่มีปัจจัยเสี่ยงแล้ว ยานี้อาจจะนำมาใช้ได้อย่างปลอดภัย

คำสำคัญ : ซิสสะพัยด์, ระหว่างจุดคิวและที, ทารกแรกเกิด

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