Effect of Cisapride on the QT Interval in Infants With Gastroesophageal Reflux

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ABSTRACT. *Objective.* **We prospectively studied the effect of cisapride per se on QT interval in young infants (3–6 months) with gastroesophageal reflux (GER) in a controlled setting.**

Study Design. **The infants diagnosed with GER and deemed to require therapy with cisapride were divided into 2 groups. Group A comprised infants with GER who underwent an electrocardiogram (ECG) before initiation of therapy with cisapride in the dose of 1 mg per kg per 24 hours, divided into 3 doses. They were reweighed after 7 to 10 days, and the dose was adjusted for their new weight. A repeat ECG was performed after ~2 weeks (12–18 days) of therapy. The QT interval was measured in each ECG and then the corrected QT interval was calculated by Bazett's formula. Group B comprised infants with GER who had already been on therapy with cisapride for over 1 month. All infants in group B received cisapride in an approximate dose of 1 mg per kg per 24 hours (.8–1.1 mg/kg/24 hours) given in 3 divided doses. They underwent only 1 ECG, ie, at 1 to 4 months after initiation of therapy. The measurement of the actual dose of cisapride was demonstrated to every parent and a marked measuring syringe was provided. The following categories of infants were not included: those with any underlying cardiopulmonary, renal, or hepatic problem; those with a history of apnea; those using a macrolide antibiotic or azole antifungal at any stage during the study; and infants hospitalized for any reason during the course of the study.**

Results. **Cisapride therapy in the dose of 1 mg/kg/day frequently resulted in a slight increase in the QT interval (pretreatment: 390 ± 18 milliseconds; posttreatment: 400 ± 20 milliseconds) but the increase was still below the accepted upper limit of 440 milliseconds and not statistically significant. Even with prolonged therapy, the pattern of change in QT interval was similar to that with therapy for 2 weeks. Overall, 2 of 100 (2%) infants developed a prolongation of corrected QT interval beyond the normal range (456 and 486 milliseconds). Neither infant had evidence of any arrhythmia or conduction defect on ECG. No additional factor could be identified in either infant to explain prolongation of the QT interval.**

Conclusion. **Our experience suggests that cautious cisapride therapy in young infants in a modest dose does not result in arrhythmias or conduction defects. We recommend that: 1) the dose of cisapride in infants be <1.2 mg/kg/day and preferably between .8 and 1 mg/kg/day; 2) the right measure of the dose be actually demonstrated to the parents; and 3) parents be provided a list of drug interactions with cisapride. One should think twice before denying the use of an effective drug simply because of the need for closer monitoring and extra time spent for parent education.** *Pediatrics* **2000;105(2). URL: http://www.pediatrics.org/cgi/content/full/105/2/e24;** ***cisapride, gastroesophageal reflux, corrected QT interval, arrhythmia.***

ABBREVIATIONS. GER, gastroesophageal reflux; ECG, electrocardiogram.

Gastroesophageal reflux (GER) is a common problem during infancy. Promotility agents like cisapride are widely used to alleviate symptomatology of GER. Recently some concern has been expressed regarding the safety of using cisapride in children and adults. The major concern has been the association of cisapride with prolongation of QT interval, which may result in ventricular arrhythmia.[1–3] In most of these cases, the common denominator has been circumstances resulting in increased serum level of cisapride either from overdose or concomitant use of drugs that inhibit cisapride metabolism or independently prolong QT interval.[2,4] We prospectively studied the effect of cisapride per se on QT interval in young infants with GER in a controlled setting.

METHODS

The infants diagnosed with GER and deemed to require therapy with cisapride were divided into 2 groups. Group A comprised of infants with GER who underwent an electrocardiogram (ECG) before initiation of therapy with cisapride in the dose of 1 mg per kg per 24 hours, divided into 3 doses. They were reweighed after 7 to 10 days and the dose was adjusted for their new weight. A repeat ECG was performed after ~2 weeks (12–18 days) of therapy. The QT interval was measured in each ECG and then the corrected QT interval was calculated by Bazett's formula.[5] Group B comprised of infants with GER who had already been on therapy with cisapride for over 1 month. All infants in group B received cisapride in an approximate dose of 1 mg per kg per 24 hours (.8–1.1 mg/kg/24 hours) given in 3 divided doses. They underwent only 1 ECG, ie, at 1 to 4 months after initiation of therapy. All infants were managed by 1 of the 3 authors. The same pediatric cardiologist who was unaware of the treatment status read all ECGs. The measurement of the actual dose of cisapride was demonstrated to every parent and a marked measuring syringe was provided.

The following categories of infants were not included: those with any underlying cardiopulmonary, renal or hepatic problem; those with history of apnea; those using a macrolide antibiotic or azole antifungal at any stage during the study; and infants hospitalized for any reason during the course of the study.

RESULTS

Table 1 shows that cisapride therapy in the dose of 1 mg/kg/day frequently resulted in a slight increase

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TABLE 1. QTc Before and After Cisapride Treatment

	Group A	Group B
Number of infants	60	40
Age in mo		
Mean (SD)	4.8 (1.1)	5.8 (1.0)
Range	3–7	3.5–7
QTc interval in milliseconds		
Before initiation of treatment		
Mean (SD)	390 (18)	
Number with QTc >440	0	
After initiation of treatment		
Mean (SD)	400 (20)	403 (27)
Number with QTc >440	1	1
Number with increase in QTc >10	30	
Number with arrhythmia	0	0

SD indicates standard deviation; QTc, corrected QT interval.

in the QT interval, but the increase was still below the accepted upper limit of 440 milliseconds and not statistically significant ($P > .05$; paired t test). Even with prolonged therapy, the pattern of change in QT interval was similar to that with therapy for 2 weeks ($P > .05$). Overall, 2 of 100 (2%) infants developed a prolongation of QT interval beyond the normal range (456 and 486 milliseconds). Neither infant had evidence of any arrhythmia or conduction defect on ECG. No additional factor could be identified in either infant to explain prolongation of the QT interval.

DISCUSSION

Our experience suggests that cautious cisapride therapy in young infants in a modest dose does not result in arrhythmias or conduction defects.

Lewin et al[1] reported a 2-month-old expremature infant with prolonged QT interval and 2:1 atrioventricular conduction while being on cisapride in the dose of 1.2 mg/kg/day. The infant was concomitantly on caffeine, ferrous sulfate, and ranitidine, none of which have been associated with a prolongation of QT interval. However, the infant was breastfed and the mother was on miconazole suppositories. Miconazole is an inhibitor of cytochrome P450 3A4 and although there is minimal systemic absorption of vaginal miconazole, it raises the possibility of a drug interaction. Hill et al[2] reported 11 children with prolonged QT interval while being on cisapride therapy, of whom 2 developed torsades de pointes ventricular tachycardia. Both of these children were concomitantly on macrolide antibiotics. Lupoglazoff et al[4] reported 7 small infants (age: 14–79 days; weight: 1.2- 4 kg; 6 of 7 were premature) with prolonged QT interval without arrhythmia while being on a large dose of cisapride (1–1.7 mg/kg/day). The QT interval returned to normal within 48 hours after the dose was reduced to a more modest dose of .8 mg/kg/day. This fits in nicely with the findings of a large study by Levine et al[6] involving 30 premature infants, none of whom had any evidence of prolongation of QT interval or arrhythmia when cisapride was given in the dose of .8 mg/kg/day.

Several features of our prospective study need to be highlighted: 1) study patients were full-term, small infants over 3 months of age, in the age group in which GER is most prevalent, cisapride most often prescribed, and cytochrome P450 3A4 levels are below adult levels,[7] so risk of toxicity is high; 2) patients had an established, reliable history and a narrow age range making the group homogenous; 3) patients served as their own controls, a method which offers a better comparison than using normal healthy controls as has been previously reported; 4) cisapride was given in a modest dose with very close follow-up and frequent monitoring and adjustment of dose; 5) all clinical conditions that could potentially increase the toxicity of cisapride were excluded. None of the drugs that prolong QT interval were given (ie, quinidine, sotalol, and procainamide). None of the drugs that inhibit cytochrome P450 3A4, thus increasing serum levels of cisapride, were concomitantly given (ie, ketoconazole, itraconazole, fluconazole, miconazole, troleandomycin, erythromycin, clarithromycin, ritonavir, indinavir, nefazodone, amitryptaline, astemizole, thioridazine, and haloperidol). Under such conditions, cisapride was not associated with any ventricular arrhythmia. Our findings support the opinion expressed in the consensus statement by the North American Society for Pediatric Gastroenterology and Nutrition, and this study responds to their recommendation for collecting more data on this issue.[8]

Finally, we would like to make the following recommendations: 1) the dose of cisapride in infants be <1.2 mg/kg/day and preferably between .8 and 1 mg/kg/day; 2) the right measure of the dose be actually demonstrated to the parents; and 3) parents be provided a list of drug interactions with cisapride. One should think twice before denying the use of an effective drug simply because of the need for closer monitoring and extra time spent for parent education.

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