Effects of Cisapride on Corrected QT Interval, Heart Rate, and Rhythm in Infants Undergoing Polysomnography

Avram Benatar, MBChB, FCP(SA), FRCPCH*; Arjen Feenstra, MD‡; Tine Decraene, MD*; and Yvan Vandenplas, MD, PhD‡

ABSTRACT. Objective. To evaluate the effects of cisapride, a prokinetic gastrointestinal drug, on the electrocardiographic QT interval, heart rate, and rhythm in infants during routine 8-hour polysomnography. Reported electrocardiogram (ECG) and rhythm disturbances in a small number of patients with the use of cisapride provided the impetus for this prospective study.

Study Design. Two hundred fifty-two infants born at term were enrolled. Of these, 134 were on cisapride therapy for suspected gastroesophageal reflux and 118 were not on cisapride and served as controls. Cisapride-treated and control infants were from the outset divided into 3 age groups; group 1: under 3 months of age; group 2: between 3 and 6 months of age; and group 3: > 6 months of age. Continuous ECG bipolar limb lead I recording, saturation monitoring, and electroencephalography were conducted. QT intervals and heart rate were measured at hourly intervals.

Results. Cisapride doses were: group 1 mean, 0.80 mg/kg/day (range: 0.38–1.55); group 2 mean, 0.80 mg/kg/day (range: 0.23–1.38); and group 3 mean, 0.72 mg/kg/day (range: 0.32–1.41). Heart rate was higher in the younger infants, with a gradual decrease with age. No difference in heart rate was detected between the cisapride and control groups. The QTc interval in patients in group 1 was statistically longer than the controls, when applying both Bazett’s and Hodges’ formulae for QT correction. The other age groups did not differ. No arrhythmia or atrioventricular conduction abnormalities were observed.

Conclusion. Infants under 3 months of age on cisapride treatment had significantly longer QTc intervals (with Bazett’s formula, the 98th percentile was 504 ms in the cisapride group vs 447 ms in controls). The clinical significance and risk of the increased QTc interval in these infants are unclear and need further evaluation and risk stratification. Meanwhile, cisapride should be judiciously prescribed in infants <3 months of age.

Cisapride, a prokinetic agent used in adults and children with gastrointestinal motility disorders, has been reported in some patients to increase the QT interval on the electrocardiogram (ECG).1-3 Prolongation of the electrocardiographic QT interval may be either congenital4-6 or acquired.7 Acquired prolongation of the QT interval can be caused by electrolyte disturbances (commonly hypokalemia and hypocalcemia), hypothermia, central nervous system injury, malnutrition, organophosphate poisoning, and medication. Medications that have been implicated include tricyclic antidepressants, macrolide antibiotics, phenothiazines, and antiarrhythmic agents.7

The QT interval on the ECG represents the period from the beginning of depolarization (QRS complex) to the end of repolarization (T wave) of the ventricles. There are at least 5 different genes responsible for the various congenital forms of long QT syndrome, and it is now clear that several different ion channels play a role in cardiac repolarization, and defects in any one of these ion channel genes can result in a long QT syndrome.8 Channel types include the voltage-gated potassium channel, outwardly rectifying potassium channel, and the voltage-gated sodium channel.7 The QT interval varies with heart rate, lengthening at slower rates and shortening at faster rates.9 The QT interval corrected for heart rate, the QTc, may be obtained by a number of formulae, one of which is Bazett’s formula.10 Normal ranges for the QTc Bazett in children have been published; the mean value of QTc remains at ~400 ms throughout all age groups. In 95% of the children, the QTc is <450 ms, and in 98% <480 ms with the exception of the first days of life, when the values are slightly higher.9 From other data on normal infants,11 taking 3 standard deviations from the mean QTc as the upper normal limit of normal, on the fourth day of life the value is 451 ms; at 2 months, 454 ms; at 4 months, 451 ms; and at 6 months, 442 ms.

Delayed cardiac repolarization, as reflected by QT prolongation on the ECG, can predispose to the occurrence of arrhythmia. Such a proarhythmic effect can degenerate into the potentially fatal polymorphic ventricular tachycardia, torsade de pointes, or even ventricular fibrillation. Cisapride can prolong the QT interval by blocking the rapid component of the delayed rectifying K+ current in the myocardium.12 Effects of cisapride on cardiac rhythm have been documented in adults and more recently in...
Two publications in 1997, 15, 16 address the issue of cisapride-associated QTc lengthening in premature neonates. Cisapride, like many other drugs, is metabolized by the cytochrome P-450 3A4 enzyme system.17 The immature cytochrome P-450 3A4 capacity reported in neonates, particularly premature infants, may predispose to high plasma concentrations of the drug or its metabolites. In addition, concurrent use of cytochrome P-450 3A4 inhibitors may also result in increased plasma levels of cisapride.18, 19

We set out to test the hypothesis of the extent and significance of the effects of cisapride on cardiac rhythm and myocardial repolarization in infants.

Given this background, the aim of our prospective study was twofold: 1) to assess the effects of cisapride on QTc interval and heart rate during an 8-hour polysomnographic examination in infants on cisapride therapy, compared with age- and sex-matched controls; and 2) to determine the incidence of arrhythmia during this 8-hour period.

METHODS

During a 24-month period, we prospectively enrolled 252 infants (born at term), admitted for routine polysomnographic study, a cardiorespiratory and neurological screening test routinely practiced in Belgium for many years.20 It is estimated that 25% to 30% of all infants in Belgium undergo a routine polysomnographic study (H. Devlieger, personal communication, 1994). None of the enrolled infants had an episode or history of an acute life-threatening event, were receiving diuretic or methylxanthine therapy, or had any previous bowel surgery. The study protocol permitted infants to be studied on only one occasion to obviate bias. Demographic data as well as a complete medical history were obtained at the time of admission. A thorough physical examination was conducted before commencing the polysomnographic recording. Infants on cisapride for a minimum of 4 days to ensure a steady-state cisapride plasma level21 were compared with a control group not receiving cisapride. Cisapride was prescribed for suspected gastroesophageal reflux. Criteria for exclusion from the study included a family history of arrhythmia or sudden death, a history of acute life-threatening event, bundle branch block on ECG, use of other medications known to prolong QTc interval, and a history of acute life-threatening event, were receiving diuretic or methylxanthine therapy, or had any previous bowel surgery. The study protocol was approved by the medical ethics committee of the Academic Hospital of the Free University of Brussels. Informed consent was given by the parents.

RESULTS

The demographic data of the patients are presented in Table 1.

Cisapride doses for the different age groups were as follows: group 1, mean: 0.80 mg/kg/day (range: 0.38–1.55 mg/kg/day and median: 0.78 mg/kg/day); group 2, mean: 0.80 mg/kg/day (range: 0.23–1.38 mg/kg/day and median: 0.80 mg/kg/day); and group 3, mean: 0.72 mg/kg/day (range: 0.32–1.41 mg/kg/day and median: 0.77 mg/kg/day). Frequency of administration varied from twice to 4 times daily.

Heart rate (Table 2) was, as expected, higher in the younger infants, showing a gradual decrease with increasing age for both the cisapride and control patients. There was no statistical difference between the heart rate of those receiving cisapride and controls in each of the different age groups. Results of the QT and corrected QT intervals are shown in Table 3 and show a significant prolongation of QTc in the group <3 months of age. For both Bazett’s and Hodges’ formulae, a significant difference in QTc was found in the cisapride patients, compared with the controls for those younger than 3 months (group 1; P < .001). However, in infants older than 3 months (groups 2 and 3), there were no significant differences in QTc interval.

Using Bazett’s formula, the 98th percentile QTc values for the controls were as follows; 447 ms for
Hodges values in milliseconds.
‡ Bazett values in milliseconds.

* months; group 3
5.
standard deviation; group 1
5, 8.4 ± 2.12
18.2 ± 3.1
37.4 ± 9.4

Weight (kg)
Group 1
n = 64
4.89 ± .69
6.24 ± 1.3
8.15 ± 1.6
Group 2
n = 35
6.89 ± 12.6
Group 3
n = 35
7.9 (5.27–13)
Mean heart rate in beats per minute, ± = standard deviation; group 1 = <3 months; group 2 = 3 to 6 months; group 3 = >6 months of age.

TABLE 3. QT and QTc intervals

<table>
<thead>
<tr>
<th>QT interval</th>
<th>Cisapride (n = 134)</th>
<th>Controls (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>n = 64</td>
<td>n = 55</td>
</tr>
<tr>
<td></td>
<td>309.5 ± 16.4</td>
<td>284.9 ± 15.9*</td>
</tr>
<tr>
<td>Group 2</td>
<td>n = 35</td>
<td>n = 32</td>
</tr>
<tr>
<td></td>
<td>301.0 ± 22.4</td>
<td>293.0 ± 18.0</td>
</tr>
<tr>
<td>Group 3</td>
<td>n = 35</td>
<td>n = 31</td>
</tr>
<tr>
<td></td>
<td>304.0 ± 17.8</td>
<td>294.0 ± 201.1</td>
</tr>
</tbody>
</table>

Bazett†
Group 1
n = 64
455.5 ± 18.7
Group 2
n = 35
427.0 ± 22.0
Group 3
n = 35
416.8 ± 18.6
Hodges‡
Group 1
n = 64
434.6 ± 14.89
Group 2
n = 35
410.2 ± 15.3
Group 3
n = 35
399.0 ± 15.8

± = standard deviation; group 1 = <3 months; group 2 = 3 to 6 months; group 3 = >6 months of age.

TABLE 2. Heart Rate by Age Group

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Cisapride (n = 134)</th>
<th>Controls (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>n = 64</td>
<td>n = 55</td>
</tr>
<tr>
<td>(weeks)</td>
<td>8.4 ± 2.12</td>
<td>8.7 ± 1.18</td>
</tr>
<tr>
<td>Group 2</td>
<td>n = 35</td>
<td>n = 32</td>
</tr>
<tr>
<td>18 (13–24)</td>
<td>18.7 ± 3.3</td>
<td>19.5 (13–24)</td>
</tr>
<tr>
<td>Group 3</td>
<td>n = 35</td>
<td>n = 31</td>
</tr>
<tr>
<td>36 (26–58)</td>
<td>43.1 ± 20.3</td>
<td>37 (25–125)</td>
</tr>
</tbody>
</table>

TABLE 1. Demographic Data

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Cisapride (n = 134)</th>
<th>Controls (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>n = 64</td>
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</table>

Bazett formula of Hodges et al.‡

percentile QTc values for the cisapride-treated groups were: 467 ms, 433 ms, and 426 ms, respectively.

The 8-hour recording was scanned for arrhythmia. No abnormality of atrioventricular conduction or evidence of ventricular ectopy was identified.

We chose to discontinue cisapride therapy in those patients with a QTc Bazett’s formula value equal to or beyond 480 ms (98 percentile for QTc Bazett, Davignon et al).²²

**DISCUSSION**

We conducted this study to determine whether cisapride, a prokinetic drug commonly used in infants, had any significant effect on the QT interval, heart rate, and rhythm when used at the recommended doses. Because all children were on cisapride before entering the study, baseline QT data are not available. We deliberately excluded patients taking other medication that may affect the metabolism of cisapride and may lead to potential toxic plasma levels. From the outset, we divided the patients into 3 age groups, because the pharmacokinetics, maturity of hepatic enzymes, and total body water content and volume of distribution within the body compartments change considerably during the first year of life. Maturation or changes in the cardiac channels with age may, theoretically, also play a role. The results of this study showed a statistically significant prolongation of the uncorrected QT and QTc interval in infants under 3 months of age receiving cisapride. However, this prolongation of QTc interval was not associated with the occurrence of rhythm disorders.

Correction of the QT interval for heart rate remains a complex and controversial area. Bazett’s formula is commonly used to correct the QT interval; however, this formula overcorrects at extreme heart rates. As a result, normal infants with relatively elevated heart rates tend to have a long QTc interval when corrected using Bazett’s formula. In contrast, the formula of Hodges et al is linear. For this reason we chose to use both Bazett’s and Hodges’ formulae to evaluate the QT interval. We chose to measure the QT intervals during an 8-hour nocturnal period to obtain a meaningful trend of the QT interval during

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steady-state plasma concentrations of the drug. In addition, this permitted an evaluation of heart rate and detection of arrhythmia over a reasonably long period of time.

The ability of cisapride to prolong cardiac repolarization is a potentially serious adverse effect and in infants younger than 3 months, cisapride seems to prolong cardiac repolarization. Excessive QT prolongation may be proarrhythmic and degenerate into potentially fatal ventricular arrhythmia, such as torsades de pointes. Cisapride, a noncardiac drug, may at high serum levels have an adverse effect on cardiac $K^+$ channels. Single cardiac myocyte experiments have demonstrated block of the delayed rectifier potassium channel ($I_{Kr}$), while in whole-heart experiments, increased action potential duration and after depolarizations were seen. These changes, related to the cisapride concentration, can result in prolongation of the QTc interval.

In addition, there are a number of substances capable of increasing cisapride plasma concentrations by inhibiting metabolism by cytochrome P-450 3A4. For this reason, all patients taking drugs metabolized by cytochrome P-450 3A4 or drugs known to prolong QTc in combination with cisapride were excluded from our study. The hepatic cytochrome P-450 3A4 enzyme is quantitatively the most important cytochrome P-450 (CYP) isoform and is responsible for the metabolism of numerous drugs, including cisapride. The cytochromes P-450 are a superfamily of haem proteins and consist of the subfamilies CYP1A, CYP2B, CYP2C, CYP2D, and CYP3A. The CYP3A subfamily comprises up to 40% of the total cytochrome P-450 content present in both the adult human liver and small intestine and consists of at least 3 isoforms in humans (ie, CYP3A4, CYP3A5, and CYP3A7) capable of metabolizing numerous drugs and endogenous substrates. Shortly after birth, a shift in activity from CYP3A7 to CYP3A4 begins to occur.

Lacroix et al demonstrated that the extent of catalytically active CYP3A4 present in the liver of infants at 1 month of postnatal age was $\sim 30\%$ of adult activity. Levels of CYP3A4 activity in infants seem to approach adult values by $\sim 6$ to 12 months of age. Furthermore, CYP3A4 is characterized by substantial intersubject variability in both hepatic enzyme content and constitutive activity. Gotschall et al provided in vitro evidence using human hepatic microsomes and heterologously expressed human cytochromes P-450 that CYP3A4 is responsible for catalyzing the biotransformation of cisapride to its major metabolite, norcisapride. Norcisapride has no intrinsic activity on myocardial conduction.

Immmaturity of cytochrome P-450 3A4 may result in poor clearance of cisapride and may be related to the effect on QTc in infants under 3 months of age observed in our study. Administration of cisapride with any drug that inhibits CYP3A4 such as the macrolide antibiotics (erythromycin and clarithromycin) and the azole antifungal agents ( ketoconazole, fluconazole, miconazole, and itraconazole) has the capacity to inhibit cisapride biotransformation and, thus, increase cisapride plasma concentration.

The relationship between the QTc interval and risk of ventricular dysrythmia if the interval is mildly prolonged is not known. Using Bazett’s formula, the risk is unknown between 440 and 500 ms. At $>500$ ms, there is a higher risk and at $>600$ ms there is a very high risk of fatal outcome. A value of 440 ms marks the limit of the top 2.5% range within the population. The risk of arrhythmia associated with a QTc of 500 ms attributable to cisapride effects on the rapid potassium-delayed rectifier current may not be the same as that attributable to a congenital abnormality of one of the potassium or sodium channels, or that caused by amiodarone or sotalol. Other factors are used to increase the predictive value of the risk of a prolonged QTc interval (family history, T wave profile, and history of syncope). The risk associated with a drug-induced prolonged QTc interval is unknown. It is not possible to predict how an individual will respond. In our study, the 98th percentile QTc value for infants under 3 months of age receiving cisapride therapy with Bazett’s formula was 504 ms, decreasing substantially beyond that age. Extrapolating to the prolonged QTc syndrome, our children under 3 months of age are at a value of unknown risk.

Several studies and case reports have now corroborated the findings of QT prolongation during cisapride therapy in children. Our data are consistent with the published reports, and highlight the potential for increased QT prolongation in the youngest age group, those less than 3 months. The clinical significance of the increased QTc interval observed in these patients and ours is unclear. In experimental studies cisapride prolongs cardiac repolarization (QT interval) without altering depolarization. Although symptomatic arrhythmia related to cisapride appear to occur infrequently, a prolonged QTc interval in the very young infants is potentially of concern. Increased QT dispersion has been advocated by some authors to be a good marker of an increased risk of ventricular arrhythmia in adult patients with heart disease, while other authors have found QT dispersion not to be a reliable marker for arrhythmic risk in children with idiopathic ventricular arrhythmia and structurally normal hearts. We could not measure QT dispersion in this study, because this necessitates the recording of 12 electrocardiographic leads. In the study by Hill and associates, only 3 of 35 children on cisapride therapy had an increased QTc dispersion. Further studies on QT dispersion in infants on cisapride therapy are required before definite conclusions can be made regarding its usefulness as a risk marker for ventricular arrhythmia.

CONCLUSION

The use of cisapride in infants older than 3 months of age is not associated with significantly longer QT intervals, compared with controls. However, infants younger than 3 months of age on cisapride have a significantly longer QT interval than that of the control group. The QTc duration in infants under 3 months of age suggests a pro-arrhythmic effect, and
judicious use of cisapride in this age group is required.

ACKNOWLEDGMENT
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