BRIEF REPORTS

Effects of Cisapride on QT Interval in Children

Amalia Tamariz-Martel Moreno, a Antonio Baño Rodrigo, a Marciano Sánchez Bayle, b Cristina Montero Luís, a María D. Acuña Quirós, c and Julia Cano Fernández d

a Sección de Cardiología Pediátrica, Hospital Universitario Niño Jesús, Universidad Autónoma de Madrid, Madrid, Spain.
b Unidad de Epidemiología Clínica, Hospital Universitario Niño Jesús, Universidad Autónoma de Madrid, Madrid, Spain.
c Sección de Gastroenterología Pediátrica, Hospital Universitario Niño Jesús, Universidad Autónoma de Madrid, Madrid, Spain.
d Sección de Lactantes, Hospital Universitario Niño Jesús, Universidad Autónoma de Madrid, Madrid, Spain.

E-mail: amtamariz@yahoo.es

Received 4 June, 2003.
Accepted for publication 27 October, 2003.

This prospective study evaluated the effects of cisapride on corrected QT interval (QTc) in infants and children.

From October 2000 to March 2003 two electrocardiograms (ECG) were obtained for 175 children (ranging in age from 1.5 months to 16.8 years), before and after 15 days of treatment with cisapride (0.2 mg/kg/dose, 3-4 times/day). A single posttreatment ECG was also obtained for 24 patients (ranging in age from 1.5 month to 15.8 years).

No statistically significant differences were found between the mean QT interval before (0.390 ± 0.018 s) and after treatment (0.391 ± 0.018 s). In patients for whom only a posttreatment ECG recording was performed, mean QTc interval was 0.399 (0.018 s). The QTc interval was never longer than 0.450 s in any of the children.

In our experience the use of cisapride at therapeutic doses in infants and children who have no associated risk factors does not significantly prolong QTc interval.

Key words: Cisapride. Children. QT interval. Arrhythmia. Tachycardia.

Full English text available at: www.revespcardiol.org

INTRODUCTION

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend cisapride as the drug of choice for chronic persistent gastroesophageal reflux in infants and children in whom symptoms persist after dietary and postural interventions.1

The drug’s safety began to be questioned in 1995 after publication of the first reported case of a prolonged corrected QT (QTc) interval and the appearance of ventricular arrhythmias in an adult being administered high doses of the drug.2 A year later, Lewin et al3 described the first pediatric case. In April 2000, actions by the Food and Drug Administration (FDA) in the United States and the manufacturer led to withdrawal of the drug from the market.4 Thereafter, its use was authorized for research programs only. In July 2000, the Agencia Española del Medicamento (Spanish Medicines Agency) restricted the use of cisapride. It was designated as a drug that may only be used in hospitals with certain defined

Efectos de la cisaprida sobre el intervalo QT en niños

Se valoró de forma prospectiva el efecto en el intervalo QT corregido (QTc) del tratamiento con cisaprida en niños.

Desde octubre de 2000 a marzo de 2003, se realizó un electrocardiograma (ECG) basal y otro a los 15 días de tratamiento con cisaprida (0.2 mg/kg/dosis, 3-4 veces/día) a 175 niños (edad entre 1,5 meses y 16,8 años). Además, se realizó un único ECG postratamiento a 24 niños (edad entre 1.5 meses y 15,8 años).

No se encontraron diferencias estadísticamente significativas entre el intervalo QTc medio basal (0,390 ± 0,018 s) y postratamiento (0,391 ± 0,018 s). En los enfermos con un único ECG postratamiento, el intervalo QTc medio fue de 0,399 ± 0,018 s. En ningún caso el intervalo QTc superó los 0,450 s.

Según nuestra experiencia, la utilización de cisaprida en dosis terapéuticas en niños sin factores de riesgo asociados no prolonga significativamente el intervalo QTc.

diagnostic capabilities and the advice given was that, before administration, electrocardiography should be carried out, and serum electrolyte levels and renal function parameters should be measured.

After this second date, we started a prospective study in our center with the twin objectives of, firstly, detecting possible QTc interval prolongation in infants and older children who had been administered therapeutic doses of cisapride and, secondly, evaluating the safety of the drug’s use in our patients.

**PATIENTS AND METHODS**

Between October 2000 and March 2003, all children who started receiving cisapride in the pediatric, gastroenterology and pulmonology departments or who were already taking the drug were referred to our department for electrocardiographic assessment of the QTc interval. None of the patients who entered the study were taking drugs that interfere with the hepatic metabolism of cisapride. A 12-lead ECG (paper speed, 25 mm/s) was recorded before administration of the medication and another was made 15 days later (mean, 17.68 days; mode, 14 days; standard deviation, 5.82 days). Two copies of each ECG were made. One was sent to the referring department and the other was used to determine the patient’s heart rate and QT interval, without it being revealed to the investigator whether the patient was taking the medication or not. All evaluations were carried out by the same individual (ATM). The values of the RR and QT intervals were calculated as the means of measurements made over three consecutive heart beats. The corrected QT interval was calculated using Bazett’s formula (i.e., QTc=QT/(square root RR). In accordance with published data, the QTc interval was regarded as normal if it was ≤0.450 s.6

Data were analyzed using the SPSS for Windows

![Figure 1. Children’s age distribution.](#)
(version 9.0.1.) statistical package. Kolmogorov-Smirnov’s non-parametric test was used to confirm that the values obtained were normally distributed. Comparison of variables was carried out using Student’s t test for paired data.

RESULTS

During the study period of 2.5 years, a total of 253 children were referred to our department. Two ECGs (i.e., before and after the start of treatment) were recorded in 175 children (95 male, 80 female). Single post-treatment evaluations were carried out in the 24 patients (14 male, 10 female) who were already taking cisapride. A total of 54 children were not included in the analysis because either only the basal ECG was available, the post-treatment ECG was made at the referring health center or hospital, or the physician in charge decided to use an alternative prokinetic drug.

Table 1 lists the clinical characteristics of the group of children studied and Figure 1 shows the children’s age distribution.

In patients in whom both basal and post-treatment ECGs were made, no statistically significant difference was found between the QT or QTc interval measured before administration of the drug and that measured after.

Table 2 summarizes the values obtained in all patients, including those in whom only the post-treatment ECG was recorded. In no patient did the QTc interval exceed 0.450 s.

DISCUSSION

Our prospective study included a greater number of patients than any previously reported study. No statistically significant differences were found between QTc interval measurements made before and after the administration of therapeutic doses of cisapride; nor was any prolongation in QTc interval detected in children in whom only a post-treatment ECG was made.

Our patients were not taking any drugs that could have interfered with the hepatic elimination of cisapride by affecting the enzymatic cytochrome complex P450 3A4, such as macrolides (e.g., clarithromycin and erythromycin), imidazole antifungals (e.g., ketoconazole, itraconazole, miconazole and fluconazole), and non-sedating antihistamines (e.g., astemizole and terfenadine). Cisapride was administered at doses that did not exceed the maximum recommended dose of 0.8 mg/kg per day.1

Our patient series did not include premature babies. These infants have an increased risk of cardiac toxicity because elevated serum concentrations of the drug and its metabolites may be present. Elevated serum concentrations are due to the immature level of hepatic elimination and to bilirubin reducing drug binding with albumin.

The control ECG was performed 15 days after the start of treatment. It could have been made any time after the second or third day of drug administration as the drug reaches a stable plasma concentration within this period. However, some authors7 report that the observed prolongation in QTc interval is greater in ECGs made after 14 days of treatment than in those made between 2 and 7 days after the start of treatment.

So far, a number of prospective studies of the effect of cisapride on QTc interval in children have been carried out, with varying results (Table 3). Some have failed to find any statistically significant prolongation in QTc interval after ingestion of the drug, whether in children carried to term or in premature infants.8-12 In contrast, others have discovered statistically significant prolongation in QTc interval in children who have been taking therapeutic doses of cisapride.

TABLE 2. Basal and Post-Treatment Electrocardiogram Measurements*

<table>
<thead>
<tr>
<th></th>
<th>Basal QT, s</th>
<th>Basal QTc, s</th>
<th>Post-Treatment QT, s</th>
<th>Post-Treatment QTc, s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children in whom both basal and post-treatment ECGs were made, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>175</td>
<td>0.29</td>
<td>0.390</td>
<td>175</td>
</tr>
<tr>
<td>Minimum</td>
<td>54.00</td>
<td>0.22</td>
<td>0.343</td>
<td>55.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>200.00</td>
<td>0.42</td>
<td>0.438</td>
<td>180.00</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>28.98</td>
<td>0.04</td>
<td>0.018</td>
<td>26.31</td>
</tr>
<tr>
<td><strong>Children in whom only the post-treatment ECG was made, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>24</td>
<td>0.28</td>
<td>0.399</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>60.00</td>
<td>0.24</td>
<td>0.360</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>165.00</td>
<td>0.40</td>
<td>0.431</td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>23.12</td>
<td>0.03</td>
<td>0.018</td>
<td></td>
</tr>
</tbody>
</table>

*HR indicates heart rate; QT, QT interval; QTc, corrected QT interval; ECG, electrocardiogram.
### TABLE 3. Prospective Studies on the Effect of Cisapride on the QTc Interval in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Cases</th>
<th>Cisapride Dose</th>
<th>Time Between ECGs</th>
<th>Effect on QT Interval</th>
<th>Arrhythmias</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine et al, 1998</td>
<td>8</td>
<td>0.2 mg/kg per dose</td>
<td>1 month Pre- and post-treatment</td>
<td>No prolongation QTc</td>
<td>None</td>
<td>QTc interval prolonged in 7 cases (13.3%)</td>
</tr>
<tr>
<td>Khoshoo et al, 2000</td>
<td>9</td>
<td>0.8-1.1 mg/kg per dose</td>
<td>12-18 days</td>
<td>No statistically significant prolongation</td>
<td>None</td>
<td>QTc interval &gt;0.450 s in 6 children (11.8%)</td>
</tr>
<tr>
<td>Ramírez-Mayans et al, 2000</td>
<td>10</td>
<td>0.2 mg/kg per dose</td>
<td>3-6 days</td>
<td>No prolongation</td>
<td>None</td>
<td>QTc interval &gt;0.450 s in 3 cases (30%)</td>
</tr>
<tr>
<td>Guía et al, 1997</td>
<td>11</td>
<td>0.6-1.2 mg/kg per dose</td>
<td>2-7 days</td>
<td>No statistically significant increase of 4%</td>
<td>None</td>
<td>QTc interval &gt;0.450 s in 6 patients (28.5%)</td>
</tr>
<tr>
<td>Hill et al, 1998</td>
<td>13</td>
<td>0.6-1.5 mg/kg per dose</td>
<td>3-7 days</td>
<td>Comparison between treatment and control group</td>
<td>None</td>
<td>QTc interval &gt;0.450 s in 8 cases (38.5%)</td>
</tr>
<tr>
<td>Khongphatthanayothin et al, 1998</td>
<td>15</td>
<td>0.6-1.5 mg/kg per dose</td>
<td>3-14 days</td>
<td>Comparison between cisapride and control group</td>
<td>None</td>
<td>QTc interval &gt;0.450 s in 10 cases (40%)</td>
</tr>
<tr>
<td>Benatar et al, 2000</td>
<td>&gt;18</td>
<td>0.2 mg/kg per dose</td>
<td>1-31 weeks</td>
<td>None</td>
<td>None</td>
<td>QTc interval &gt;0.450 s in 10 cases (40%)</td>
</tr>
</tbody>
</table>

**Ankyrins**

- None: No report of ankyrin expression levels
- None: No report of ankyrin genotyping

**Comments**

- QTc interval >0.450 s in 6 cases (11.8%)
- QTc interval >0.450 s in 6 patients (28.5%)
- QTc interval >0.450 s in 8 cases (38.5%)
- QTc interval >0.450 s in 10 cases (40%)
significant prolongations.\textsuperscript{6,7,13-17} It is worth emphasizing that only one study\textsuperscript{14} has reported the occurrence of arrhythmias in association with QTc interval prolongation. This was observed in two children who were simultaneously receiving a macrolide compound.

A retrospective study carried out by Ward et al\textsuperscript{18} found only three cases of arrhythmias, all non-lethal, among 11,000 premature babies who were being treated with cisapride. Two of these cases were associated with overdoses and one with erythromycin co-administration.

According to Markiewicz and Vandenplas,\textsuperscript{19} there have been no reports of fatal arrhythmias in healthy children who were being treated with appropriate doses of this drug. Moreover, they note that the occurrence of torsade de pointes ventricular tachycardia is associated with cisapride overdose or with the concomitant administration of drugs that interfere with cisapride elimination.

The results of our study add further support to the view that the administration of cisapride in normal therapeutic doses does not significantly prolong the QTc interval in infants and older children.

**ACKNOWLEDGMENTS**

We wish to express our thanks to María Ángeles Fernández Fernández and Julia Fernández-Yruegas Moro for performing the electrocardiograms.

**REFERENCES**