Effects of Cisapride on QT Interval in Children

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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 QTc 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.*

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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.

Palabras clave: *Cisaprida. Niños. Intervalo QT. Arritmia. Taquicardia.*

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 al[3] 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

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TABLE 1. **Clinical Characteristics of the Group of Children Studied***

	Age, years	Weight, kg	Height, cm	SP, mm Hg	DP, mm Hg
Children in whom both basal and post-treatment					
ECGs were made, n	175	175	174	169	169
Mean	3.62	17.487	91.47	101.31	55.60
Minimum	0.13	2.440	50.00	55.00	29.00
Maximum	16.81	113.500	168.50	131.00	99.00
Standard deviation	4.02	16.222	29.99	13.08	10.39
Children in whom only the post-treatment					
ECG was made, n	24	22	22	19	19
Mean	1.84	11.712	76.66	100.00	51.89
Minimum	0.10	4.050	55.00	82.00	27.00
Maximum	15.77	64.200	165.60	115.00	75.00
Standard deviation	3.70	13.231	27.25	9.36	12.70

*SP indicates systolic arterial pressure; DP, diastolic arterial pressure; ECG, electrocardiogram.

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.[5]

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

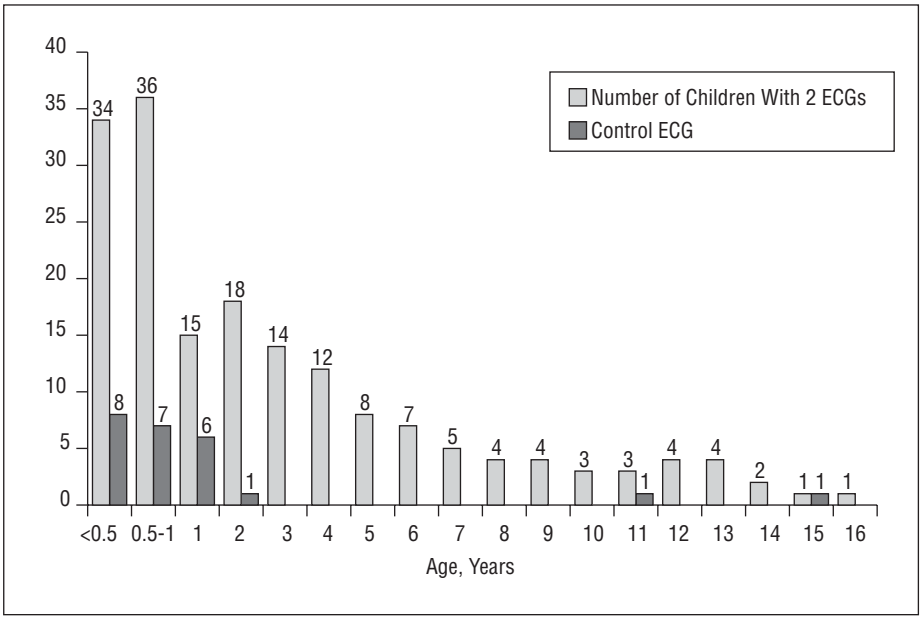

Figure 1. Children's age distribution.

(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., ketokonazole, 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 authors[7] 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

TABLE 2. **Basal and Post-Treatment Electrocardiogram Measurements***

	Basal HR, beats/min	Basal QT, s	Basal Qtc, s	Post-Treatment HR, beats/min	Post-Treatment QT, s	Post-Treatment Qtc, s
Children in whom both basal and post-treatment ECGs were made, n	175	175	175	175	175	175
Mean	113.74	0.29	0.390	111.24	0.29	0.392
Minimum	54.00	0.22	0.343	55.00	0.22	0.346
Maximum	200.00	0.42	0.438	180.00	0.42	0.433
Standard deviation	28.98	0.04	0.018	26.31	0.04	0.018

	Post-Treatment HR, beats/min	Post-Treatment QT, s	Post-Treatment Qtc, s
Children in whom only the post-treatment ECG was made, n	24	24	24
Mean	127.08	0.28	0.399
Minimum	60.00	0.24	0.360
Maximum	165.00	0.40	0.431
Standard deviation	23.12	0.03	0.018

*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**

Study	Type	Number of Cases	Cisapride Dose	Time Between ECGs	Effect on QTc Interval	Arrhythmias	Comments
Levine et al, 1998[8]	Prospective, controlled	30 children (10 premature babies of 25–36 weeks' gestation)	0.2 mg/kg per dose for 4 doses/day	1 month, Pre-and post-cisapride comparison	No prolongation QTC	None	–
Khoshoo et al, 2000[9]	Prospective, controlled	children 3-6 monts Group 1 (n= 60) ECGs before treatment and 15 days after Group 2 (n= 40) ECGs 1 month after treatment	0.8-1.1 mg/kg/ per day in 3 doses	12-18 days Pre-and post-cisapride comparison	No statistically significant prolongation	None	2 children (1 in each group), had a QTc >0.440 s
Ramírez-Mayans et al, 2000[10]	Prospective, controlled	63 children (1 month-18 years) and 57 control	0.2 mg/kg/ per doses for 3 deses/day	Before 15 days after stopping treatment	Prolongation observer with and without cisapride no statistically significant differeces between groups	None	QTc interval prolonged in 5 treated and 6 control subjects
Guala et al, 2000[11]	Prospective, controlled	31 children (1.5-20 monts)	0.8 mg/kg/day (0.67-0.85mg/kg/day) in 4 doses	5 days pre-and cisapride comparison	No prolongation	None	–
Levy et al, 2001[12]	Prospective randomized, double-blind, controlled	49 children (6 monts-4 years)	0.2 mg/kg/doses	3-8 weeks 3 doses/day or placebo and placebo	No prolongation comparison between cisapride	None	–
Bernardini et al, 1997[13]	Prospective, controlled	49 neonates of 25-41 weeks' gestation	0.84 mg/kg/day (0.42-1.6mg/kg/day)	3 days pre-and post-cisaprine comparison	Statistically significant prolongation, no correlation with Gestational age or birth weight	None	QTc interval >0.450 s in 7 cases (14.3%)
Hill et al, 1998[14]	Prospective, controlled	35 children (0.4-18 years) 1000 control subjects	0.67 mg/kg/day (0.30-1.68mg/kg/day)	Comparison between treatment and control group	31% treated patients (n=11) had QTc interval >0.450 s	2 (who were taking macrolides) had torsade de pointes ventricular tachycardias	–
Khongphatthanayothin et al, 1998[15]	Prospective, controlled	30 children with pre-and posd-cisaprine ECGs; 71 children with post-cisapride ECGs	0.6-1.2 mg/kg/day	2-7 days pre- and post-cisaprine comparison	Statistically significant significant increase of 4%	None	12 (11.8%) had QTc intervals >0.440 s all of which had associated risk factors
Benatar et al, 2000[6]	Prospective, controlled	134 received treatment; 3 groups (<3 months, 3-6 months, and >6 months); 118 control subjets	0.8 mg/kg/day (0.38-1.55mg/kg/day)	Comparison between treated (for at least 4 days) and controls	Statistically significant prolongation in group treated for <3 months	None	QT measurement made by polysomnography
Semama et al, 2000[16]	Prospective, controlled	21 full-term neonates	0.2 mg/kg/ per doses for 4 doses/day	2,7, and 14 days pre-and post-cisapride comparison	Statistically significant prolongation that increased with treatment duration	None	QTc interval >0.450 s in 6 patients (28.5%)
Cools et al, 2001[7]	Prospective, controlled	10 premature babies	0.2 mg/kg/ per doses for 4 doses/day	72 hours, pre- and post-cisapride comparison	Statistically significant increase that was inversely related to postnatal age	None	No effect on QTc dispersion
Dubin et al, 2001[17]	Prospective, controlled	25 premature babies group A – gestational age <31 weeks; Group B – gestational age >31 weeks	0.1-0.2 mg/kg/ doses for 4 doses/day	30-60 hours, pre- and post-cisapride comparison	8 cases (32%) with QTc interval >0.450 s; 10 cases (40%) with prolonged QTc interval	None	QTc interval prolongation greater in group A

significant prolongations.[6,7,13-17] It is worth emphasizing that only one study[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[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,[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.

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