Effects of Cisapride on QTc Interval in Children

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Abstract

Objective: Cisapride is a prokinetic drug with different reports on its cardiac side effects. As there might be a genetic susceptibility for the effects of this drug, we studied its effects on QTc interval of children in our region.

Material & Methods: This semi-experimental study was performed on children aged over one month, who attended Amirkola Children's Hospital from October 2004 to March 2005 and needed to be treated with Cisapride. Patients with risk factors such as cardiac disease, electrolyte disturbance and drug usage interfering with Cisapride metabolism were excluded from the study. Cisapride was prescribed orally 0.6mg/kg/day in 3 doses. ECG was taken in lead II before drug administration and after one week. QTc intervals before and after treatment were compared. P-value > 0.05 was considered significant.

Findings: Among 135 admitted children needing Cisapride, 118 cases fulfilled inclusion criteria and were enrolled in the study. Their mean age was 14.1 (1.5) months. The mean QTc intervals before and after treatment were 377 (20) msec and 380 (22) msec, respectively (P=0.1). No child had a QTc interval more than 450 msec.

Conclusion: Cisapride (0.6mg/kg/day) did not cause a significant prolonged QTc interval in children with no risk factor.

Key Words: Cisapride, Children, QTc interval, Arrhythmia, Gasteroesophageal reflux.

Introduction

Cisapride is a benzamide derivative that with its 5-HT4 receptor agonist, 5HT3 antagonistic and anti-dopaminergic characteristics and its effect on post-ganglionic receptors, causes an increase in Acetyl choline (Ach) release which acts as a prokinetic[1,2]. This drug has been
recommended in the treatment of resistant gastroesophageal reflux diseases (GERD), intestinal pseudo obstruction, neonatal nutrition intolerance, chronic constipation and functional dyspepsia\cite{1-6}. Among these, Cisapride has been widely used in GERD, as the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended Cisapride as the drug of choice in infants and children with persistent GERD symptoms and no response to nutritional or postural treatments\cite{7}. In 1995, the first report of prolonged corrected QT (QTc) interval and ventricular arrhythmia in an adult following receiving a high dose of the drug, raised the question of its safety\cite{8}. The first similar case was reported in the children the following year\cite{9} and from the year 2000, the food and drug administration in the USA, has authorized its usage only in research programs\cite{2,10}. On the other hand, there are several studies with different reports afterwards\cite{6,11}. There are limited studies on cardiac complications of Cisapride in our country.

Regarding the conflicting results for the incidence of cardiac complications in Cisapride administration and a probable genetic cause for this complication, we studied the effect of Cisapride on QTc interval of Iranian children admitted to our children’s hospital.

Material & Methods

This prospective study was carried out in children aged over one month, who attended Amirkola Children’s Hospital in north of Iran, from October 2004 to March 2005 and needed to be treated with Cisapride. After taking the patient’s history, physical examination and obtaining the permission of the parents, patients were enrolled in the study. Primary ECG was taken as a long lead II (25mm/s speed and 1mv voltage, standard) and then Cisapride (Jansson Gilag corporation, Belgium) was administered orally, 0.2mg/kg every 8 hours. A second ECG was taken under the same conditions, after week. The mean QTc interval before and after treatment was compared using Bazett’s formula (QTc=QT/√RR) by a pediatric cardiologist.

Patients with the following risk factors were excluded from the study: known cardiac disease or electrolyte disturbance, co-administration of drugs interfering with Cisapride metabolism such as macrolides, antihistamines or antifungal drugs, primary ECG disturbance or not using the drugs correctly.

Data were analyzed using SPSS statistical software and Mann-Whitney and Paired t-tests. P-value less than 0.05 were considered significant.

Findings

Among 135 cases were enrolled with respect to history and physical examination; 17 cases were excluded, one due to an arrhythmia in the primary ECG and 16 because of poor follow up or inappropriate drug administration. The mean (SD) age of the remaining 118 cases was 14.1 (1.5) months. Sixty five (55.1%) cases were boys and 53 (44.9%) girls with mean age 14.6 and 13.3 month, respectively. The mean QTc interval before treatment was 377 (20) msec and 380 (22) msec after the treatment (P=0.1). Before treatment the mean (SD) QTc was 378 (22) and 374 (19) msec in boys and girls respectively (P=0.3), which turned to 382 (21) and 378 (22) msec after the treatment (P=0.319). The mean (SD) QTc before and after treatment in children less than one year old was 374 (19) msec and 380 (22) msec respectively (P=0.058), whereas children aged over one year showed a mean (SD) QTc of 381 (22) msec before and 382 (21) msec after the treatment (P=0.9). No case had a QTc interval longer than 450 msec.
Discussion

This study showed that QTc interval had no significant difference before and after Cisapride administration, though our patients had no arrhythmogen risk factors such as cardiac disease, electrolyte imbalance or co-administration of the drugs that affect cytochorome complex P450 and thus hepatic clearance of Cisapride.

There are several studies with the same finding as ours. In Bozkurt and colleagues’ study on 28 children with developmental retardation and gasteroesophageal reflux in Turkey, in Amalia Tamariz’s study on 185 children of 1.5-16 years old in Spain, as well as Khorana's study on 20 newborns in 2003 in Thailand and Levy's research on children from 6 months to 6 years old in 2001 in New York, No one shows a significant difference in QTc intervals before and after Cisapride administration; likewise our study, the patients had no mentioned risk factors.[11-14]. On the other hand some other studies showed a significant QTc prolongation after Cisapride usage[15,16], which can be suggestive of a background or genetic susceptibility.

Drug dosage can also affect the QTc prolongation and the incidence of arrhythmia. Wang and colleagues in Taiwan studied 75 adult patients in which Cisapride administration of 5 mg 3 times a day made no significant difference in QTc interval, whereas an increased dosage to 10 mg 3 times a day prolonged QTc significantly[17]. Mojtahedzadeh and colleagues observed 2 cardiac complications in their study on 54 infants[18], noticing that their patients received the drug up to 1 mg/kg/day, while in our study the top dose was 0.6 mg/kg/day. Cool’s study on premature neonates showed that the blood level of the drug was higher when prescribed 0.1 mg/kg every 3 hours in comparison to 0.2 mg/kg every 6 hours[19].

Age had no effect on Cisapride-dependent QTc prolongation in our study, as QTc interval had no significant difference in children aged less than or over one year. Though in Benatar’s study, it has been found that in infants less than 3 months of age receiving Cisapride 0.8 mg/kg/day, drug plasma level was higher and Qtc was longer in comparison to other ages[20]. Kohl found QTc to be longer in premature neonates and ELBW comparing to other newborns, while Zamorasa’s study showed a longer QTc interval in preterm newborns in comparison to term ones[6,21]. Considering these studies, it seems that in lower age especially in preterm newborns, QTc interval is more affected by Cisapride therapy due to a difference in drug metabolism.

Conclusion

Based on our study, Cisapride (0.6 mg/kg/day) did not cause a significant prolonged QTc interval in children with no risk factors such as known cardiac disease, electrolyte disturbance or co-administration of drugs interfering with cisapride metabolism.

References


