

Effects of cisapride on QTc interval in neonates

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Abstract

Aim—Prospective survey of the effects of cisapride on QTc interval in neonates given cisapride.

Methods—QTc interval was determined just before and 2.9 (0.9) days after outset of the treatment in 49 neonates treated with cisapride between 1 August 1995 and 29 February 1996.

Results—Cisapride significantly increased QTc interval ($p = 0.0001$), and this was higher when birthweight or gestational age were lower. The prolongation of QTc interval above the arbitrary value of 0.450 ($n = 7$) was clinically asymptomatic and was significantly more common in the infants born with a gestational age ≤ 33 weeks ($n = 6$).

Conclusion—The findings indicate that cisapride accumulates in less mature neonates. Further pharmacokinetic studies are needed.

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Keywords: cisapride; QT interval; QTc interval

Cisapride is a prokinetic agent used in adults' and children's gastrointestinal motility disorders. Despite the lack of pharmacokinetic studies, this drug is widely used in neonates. The currently recommended dose in neonates and infants is 0.15 to 0.3 mg/kg three to four times a day.¹⁻³ Although cisapride is regarded as a safe and well tolerated drug, increased heart rate corrected QT (QTc) interval has been reported in adults^{4,5} and in one neonate⁶ treated with cisapride.

Similarly, we recently observed a neonate with a prolongation in QTc interval induced by cisapride. This prompted us to conduct a prospective survey to determine the prevalence of such an occurrence.

Case report

A child was born at 31 weeks of gestational age with a birthweight of 1330 g. The Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. He was admitted to the neonatal intensive care unit at Dijon because of respiratory distress syndrome and neonatal infection. He was mechanically ventilated from days 1 to 4.

On day 17 he was treated with cisapride (0.21 mg/kg) every 6 hours and sodium alginate for gastro-oesophageal reflux. He also received caffeine to prevent apnoea. From days 23 to 29 miconazole was applied locally to the skin.

On day 31 an electrocardiogram was performed so that diphemanil methylsulfate could

be prescribed. The ECG showed a prolonged QTc interval (0.490) calculated by the Bazett formula.

Serum potassium and serum calcium concentrations were within the normal range and a cerebral computed tomogram did not reveal any intracranial haemorrhage. The evoked audiometry response was normal. There was no family history of syncope, sudden death, or deafness.

The QTc interval prolongation was confirmed by two successive ECGs performed on days 32 (0.489) and 36 (0.500). Cisapride was subsequently withdrawn on day 40. This was followed by a decrease in QTc interval to 0.414 by day 43 and to 0.419 by day 45. The reintroduction of cisapride on day 48 was associated with an increase in QTc interval two days later (0.476). Cisapride treatment was stopped on day 50 and QTc interval returned to normal values on day 54 (0.389) and remained in the normal range at 4 months of life (0.402).

This case strongly suggested that cisapride could induce asymptomatic QTc interval prolongation in premature neonates. We therefore decided to observe prospectively the effects of cisapride on QTc interval in all neonates given the drug in our department.

Methods

From 1 August 1995 to 29 February 1996 all neonates treated with cisapride were included in this open survey. For each infant, birthweight, gestational age, postnatal age, postconceptional age, weight on the day of start of treatment and associated treatments were recorded. Exclusion criteria for QTc interval analysis were: increased QTc interval (> 0.450) before cisapride administration or recognised conditions associated with an increase in QTc interval,⁷ such as hypocalcaemia, hypokalaemia, hypothyroidism, intracranial disorders and certain drugs,^{7,8} or those contraindicated during treatment with cisapride (ketoconazole, fluconazole, itraconazole, miconazole, erythromycin, clarithromycin, or troleandomycin).⁹

The ECGs were performed just before and 3 days after starting treatment with cisapride, using a Hellige simpliscriptor EK 31 or a Hewlett Packard PageWriter XLs model M1705A, with a paper speed of 25 mm/seconds. QTc interval was calculated as:

$$\frac{QT}{\sqrt{RR}}$$

in five beats using lead II and these five values were then averaged. Each ECG was read blind by two people. A QTc interval higher than the arbitrary value of 0.450 was regarded as significant.¹⁰

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A blood test for potassium and calcium concentrations and a cranial sonogram were available for all the infants with an increase in QTc interval above 0.450 after cisapride treatment began. Serum potassium and serum calcium concentrations below 3.5 mmol/l and 2.10 mmol/l, respectively, were regarded as abnormal. Congenital hypothyroidism was excluded in all infants by the determination of serum thyrotropin concentration on day 3, in accordance with the French neonatal screening programme.

Each infant acted as its own control. QTc intervals before and after cisapride were compared using the Wilcoxon signed rank test. Linear regression was used to analyse the relation between QTc interval before treatment and gestational age; changes in QTc interval (Δ QTc) and other variables (birthweight, weight at the start of treatment, gestational age and postconceptional age). Comparisons among subgroups were performed using the χ^2 test or the Mann-Whitney U test, as needed. P values of < 0.05 were considered significant. All data were expressed as means (SD).

Results

Fifty one infants were enrolled in the survey. Two infants were subsequently excluded because of intraventricular haemorrhage in one and simultaneous treatment with erythromycin in the other. The mean birthweight and gestational age were 2240 (1003) g (range 820–4200) g and 34.6 (4.8) weeks (range 25–41 weeks), respectively. The distribution of the gestational age of these infants is shown in figure 1. On the first day of cisapride treatment, mean postnatal and postconceptional ages were 12.4 (9.7) days (range 1–43 days) and 36.3 (4.9) weeks (range 26–46.1 weeks), respectively. Mean weight at the outset of treatment was 2271 (986) g (range 730–4290) g. The mean dose of cisapride was 0.84 (0.17) mg/kg/day (range 0.42–1.6 mg/kg/day) administered four times daily.

QTc interval was measured just before and 2.9 (0.9) days (range 2 to 6 days) after starting cisapride. QTc interval values obtained by the two readers were not significantly different (median of the variation between the two readings: 1.1%; range from –11.8% to 9.2%). The two readings were therefore averaged for each QTc interval. There was no correlation between QTc interval before cisapride and gestational age or birthweight.

The initiation of cisapride induced a significant increase ($p = 0.0001$) in QTc interval from 0.395 (0.020) (range 0.356–0.446) to 0.418 (0.031) (range 0.371–0.504).

QTc interval increased above the arbitrary value of 0.450 in seven infants treated with cisapride. These QTc interval values were: 0.465; 0.468; 0.473; 0.474; 0.475; 0.478; and 0.504. None of these infants had clinical symptoms related to QTc interval prolongation. Six of the infants had a gestational age of ≤ 33 weeks (fig 1). The risk of prolonging the QTc interval above 0.450 was significantly increased in this group. Furthermore, infants with a QTc interval above 0.450 had both significantly lower

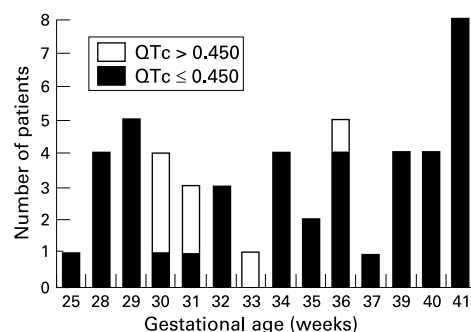


Figure 1 Distribution of neonates enrolled in the survey according to gestational age: □ patients with QTc interval above 0.450 after treatment with cisapride; ■ patients with no QTc interval increase above 0.450 after treatment with cisapride.

weight at the start of treatment and higher Δ QTc compared with the rest of the study group. There was no significant difference between these two subgroups with regard to the length of QTc interval before cisapride, birthweight, postconceptional age, postnatal age and dose of cisapride.

We also failed to find any correlation between Δ QTc and the daily dose of cisapride given, postnatal age, and postconceptional age. However, Δ QTc showed a weak but significant inverse correlation with gestational age ($r^2 = 0.128$; $p = 0.012$), birthweight ($r^2 = 0.149$; $p = 0.006$), weight at the beginning of cisapride treatment ($r^2 = 0.128$; $p = 0.011$), and QTc interval before treatment ($r^2 = 0.0099$; $p = 0.028$).

Discussion

The effects of cisapride on heart rhythm have recently come to light. The first reported effects included tachycardia.^{11–13} From September 1993 to April 1996, the Food and Drug Administration's MedWatch Reporting Program (spontaneous reporting system) was sent 23 cases of QT interval prolongation in patients taking cisapride. Most of those patients were chronically ill, had other potential risk factors for arrhythmias, or were receiving a cocktail of drugs.⁹

In 1995 Janssen Pharmaceuticals warned physicians in the USA about two cases of ventricular arrhythmias, including torsades de pointes in patients treated with both cisapride and ketoconazole.⁵ The same year, the first published case of increased QTc interval assigned to cisapride was reported in a 64 year old man treated with high doses of cisapride for a diabetic gastric atony. The QTc interval increase (0.550) was revealed as a result of syncope. When cisapride was gradually reduced, the QTc interval returned to normal.⁴

In 1996 Lewin *et al*⁶ reported the first cisapride induced QTc interval increase in a neonate. This infant was born at 30 weeks of gestational age and presented at 2 months of age with a 2:1 atrioventricular conduction with a prolonged QTc interval of 0.510. He had been prescribed cisapride at a dose of 0.3 mg/kg four times a day. Once cisapride was discontinued, the QTc interval reverted to normal.

Our index case indicates a role for cisapride in the prolongation of QTc interval because treatment was associated with QTc interval increases which stopped once its use had been discontinued. The prolongation of QTc interval could not be ascribed to a cisapride-miconazole interaction because absorption of cutaneous application of miconazole is poor and especially because the QTc interval was still increased 10 days after miconazole had been discontinued.

Our prospective survey has confirmed and extended those limited observations. It has shown that cisapride increased QTc interval and that this increase was higher when the birthweight or gestational age were low. Moreover, a QTc interval exceeding 0.450 was observed in 14.3 % of the 49 neonates treated with the drug and this was mainly observed in neonates with a gestational age of ≤ 33 weeks (six out of seven neonates).

The recent demonstration of a dose dependent class III anti-arrhythmic effect of cisapride on the Purkinje fibres of rabbits,¹⁴ suggests that the increase in QTc interval with cisapride might have been due to an accumulation of the drug. Cytochrome P-450 3A4 enzyme system affects cisapride metabolism,⁹ so we hypothesise that the limited cytochrome P450 function reported in neonates, particularly premature infants,¹⁵ could predispose to high plasma concentrations of the drug, and/or accumulation of its active metabolites, and/or a production of toxic metabolites by modified metabolic pathways. This hypothesis is strengthened by the interaction of ketoconazole, which inhibits cytochrome P-450 3A4,^{16,17} with cisapride metabolism.^{5,9} Moreover, the positive correlation described between the biotransformation capacity of the liver and gestational age¹⁸ could explain why the QTc interval prolongation above 0.450 was observed only in premature

infants in our survey. Pharmacokinetic studies are therefore mandatory in newborn infants in order to establish a safe therapeutic dose regimen for this particular group.

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