

Effects of cisapride on QTc interval in term neonates

D S Semama, S Bernardini, S Louf, B Laurent-Atthalin, J-B Gouyon

Abstract

Background—Cisapride administration for 48 hours has been shown to increase heart rate corrected QT (QTc) interval in preterm neonates. Accumulation of the drug because of liver enzyme immaturity has been suggested to be the reason. If this is correct, a longer survey of QTc interval should disclose an increase even in term neonates.

Objective—A prospective survey of the effects of cisapride on QTc interval in term neonates administered cisapride.

Setting—Neonatal Unit of the University Hospital of Dijon, France.

Design—QTc interval was determined just before and 48 hours, seven days, and 15 days after the start of treatment.

Subjects—Twenty one term newborn infants (mean gestational age 39.3 weeks) given the recommended dose of cisapride (0.2 mg/kg, four times a day).

Results—Administration of cisapride caused a significant increase in QTc interval ($p < 0.01$). The mean value increased from 0.397 before treatment to 0.418 after 48 hours, 0.431 by day 7, and 0.447 by day 15. A QTc interval exceeding 0.450 was found in six neonates: three at 48 hours, one at day 7, and two at day 15. In two infants, withdrawal of the drug was associated with normalisation of the QTc interval.

Conclusions—These results support the hypothesis of cisapride accumulation in newborns due to enzymatic immaturity and indicate that QTc interval should be monitored in neonates receiving this drug. (*Arch Dis Child Fetal Neonatal Ed* 2001;84:F44-F46)

Keywords: heart; cisapride; QT interval; QTc interval; neonate; term

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toxic metabolites by modified metabolic pathways". We concluded that pharmacokinetic studies were mandatory in newborn infants to establish a safe therapeutic dosage regimen in this particular population.¹

In 1997, the Janssen Cilag company warned doctors that Prepulsid suspension (1 mg/ml) should not be used in preterm infants. More recently, Vandenplas *et al*² proposed the use of a starting dose of 0.1 mg cisapride/kg, four times a day, in premature babies. They also recommended that the QTc interval be determined before initiation of cisapride treatment and then three days later in this particular population. However, no specific recommendations were proposed for term neonates.

If the hypothesis of drug accumulation because of enzymatic immaturity is right, we speculated that a longer survey of the QTc interval would disclose an increase in that interval even in term neonates, in whom cytochrome P450 function is also limited.² Therefore we have conducted a prospective survey which shows that the cisapride induced prolongation of the QTc interval is also common in term neonates and is usually asymptomatic.

Patients and methods

All term newborn infants treated with cisapride in our neonatal unit from 1 July 1997 until 31 January 1998 were included in this open survey. For each infant, birth weight, gestational age, postnatal age, postconceptional age, weight on the day of the start of treatment, and associated treatments were recorded. Exclusion criteria for QTc interval analysis were either increased QTc interval (> 0.450) before cisapride administration or existence of well known conditions that could increase the QTc interval,⁴—for example, hypocalcaemia, hypokalaemia, hypothyroidism, intracranial disorders, and the concomitant prescription of drugs known to increase the QTc interval⁵ or drugs that Janssen Pharmaceutica warned doctors not to prescribe concomitantly with cisapride (ketoconazole, fluconazole, itraconazole, miconazole, erythromycin, clarithromycin, troleandomycin).⁶

Electrocardiograms were performed just before and 48 hours, seven days, and 15 days after initiation of cisapride treatment, if infants were still in hospital being treated at that time. The electrocardiograms were performed with a Hewlett-Packard PageWriter 100 model M1705B, with a paper speed of 50 mm/second to allow a precise measure of QTc interval. QTc interval was calculated as QT/\sqrt{RR} in five non-consecutive beats using lead II, and the five values were then averaged. Each electrocar-

Cisapride is a gastrointestinal prokinetic agent that is widely used in neonates. We have previously shown that its administration in neonates for 48 hours is associated with an increase in heart rate corrected QT (QTc) interval and that this increase is higher when the birth weight or the gestational age is low.¹ Moreover, a QTc interval exceeding 0.450 was observed in seven of the 49 cisapride treated neonates, mainly those with gestational age below 33 weeks (six of the seven).¹ We hypothesised that the limited cytochrome P450 function reported in newborns, particularly the premature infant,² "could predispose to high plasma concentrations of the drug, and/or accumulation of its active metabolites, and/or a production of

diagram was initially read by the doctor in charge of the neonate and was secondarily read by two blinded readers. According to the literature, a QTc interval higher than 0.450 was considered significant.⁷

A blood test for potassium and calcium levels was available for all the infants included in the survey. A serum potassium concentration lower than 3.5 mmol/l and a total serum calcium concentration lower than 2.10 mmol/l were considered to be pathological. Congenital hypothyroidism was excluded in all infants by dosage with thyrotrophin on day 3, as part of the French neonatal screening procedure.

Each infant acted as its own control. Comparisons between QTc interval before and after cisapride were performed by analysis of variance followed by the Fisher LSD test. Inter-subgroup comparisons were performed by the Mann-Whitney U test. $p < 0.05$ was considered statistically significant. All data are expressed as means (SD).

Results

Twenty one infants were enrolled in the survey. No infant was secondarily excluded. Mean birth weight and mean gestational age were 3065 (579) g (range 1700–4180) and 39.3 (1.4) weeks (range 37–41) respectively. On the first day of cisapride treatment, mean postnatal and postconceptional age were 6.4 (4.9) days (range 1–19) and 40.2 (1.8) weeks (range 37–43) respectively. Mean weight at the outset of treatment was 3014 (657) g (range 1630–3960). The mean dose of cisapride was 0.19 (0.01) mg/kg (range 0.18–0.21) administered four times a day.

The values obtained by the two blinded readers for QTc interval were not statistically different (median of the variation between the two readings 0.5%; range from -5.0% to 4.3%). Therefore the two readings were averaged for each QTc interval.

Initiation of cisapride treatment induced a significant increase ($p < 0.01$) in QTc interval from 0.397 (0.021) (range 0.335–0.423) before treatment ($n = 21$) to 0.418 (0.028) (range 0.375–0.460) at 48 hours ($n = 21$), 0.431 (0.023) (range 0.386–0.461) at day 7 ($n = 14$), and 0.447 (0.038) (range 0.414–0.515) at day 15 ($n = 7$). The QTc interval increased to above 0.450 in six cisapride treated infants. These QTc intervals were: 0.457, 0.459, 0.460, 0.460, 0.461, 0.471. None of these infants had clinical symptoms related to QTc interval prolongation. Infants with an increased QTc interval above 0.450 had a statistically higher QTc interval before treatment than the 15 oth-

ers (0.413 (0.01) *v* 0.390 (0.02); $p < 0.05$). Comparison between these two subgroups failed to show any statistical difference for gestational age, birth weight, postconceptional age, postnatal age, and weight at the outset of treatment. It is interesting to note that the significant increase in QTc interval, described above, remains even if the six patients who developed a QTc > 0.450 are eliminated from further analysis.

Only two of these six infants had been initially identified by the doctors in charge of these neonates (table 1; patients nos 4 and 6). The four remaining infants (1, 2, 3, 5) were not found to have increased QTc interval before the double blind reading of electrocardiograms. Table 1 shows the evolution of QTc interval of the six infants for whom double blind reading of the electrocardiogram showed an increase in QTc interval above 0.450.

Discussion

These results confirm that recommended doses of cisapride can increase QTc interval even in term neonates. These doses have been shown to induce a range of plasma concentrations similar to that reported in adults.⁸ Prolongation of treatment was associated with a significant and progressive increase in the mean value of this interval from 0.397 before treatment to 0.447 at day 15 ($p < 0.01$). This total dose dependent increase in QTc interval supports the hypothesis of liver enzyme immaturity with subsequent accumulation of the drug, which has been shown to lengthen QTc by a direct effect on the human ether-a-go-go related gene (HERG), human cardiac K⁺ channel.⁹ Moreover, prolongation of this interval above 0.450 is also both common (29%) and clinically asymptomatic in term neonates. This increase in QTc interval remains even if the six patients who developed a QTc > 0.450 are eliminated from further analysis, suggesting that there is no evidence for genetic susceptibility to QT prolongation with cisapride administration.

In addition to verification of a relation between cisapride administration and QTc interval prolongation even in term neonates, our study discloses two important issues. For two infants (nos 3 and 5), the QTc interval spontaneously returned to 0.450. This result could be explained by intraindividual variations in QTc interval, a consequence of modification of sympathetic and parasympathetic tone.¹⁰ Moreover, it has been reported that the increase in QTc interval during the neonatal period may be only transient.^{7 11} Schwartz *et al*⁷ reported 35 cases of increased QTc interval out of 3946 electrocardiograms performed in 4 day old neonates. Thirty two infants were observed: 30 spontaneously normalised their QTc interval, but two died because of sudden infant death syndrome. However, the increase in QTc interval observed in our patients cannot be considered a transient phenomenon independent of cisapride administration because (a) experimental¹² and clinical^{1 13–15} studies have already confirmed the relation between cisapride and QTc interval prolongation, (b) our

Table 1 Evolution of QTc interval during cisapride administration over 15 days in the six infants with a QTc value above 0.450 (double blind reading)

Patient	QTc before cisapride	QTc at 48 hours	QTc at day 7	QTc at day 15	Cisapride stopped?	QTc after withdrawal
1	0.423	0.457	0.453	—	No	—
2	0.421	0.396	0.447	0.460	No	—
3	0.409	0.459	0.439	—	No	—
4	0.422	0.443	0.443	0.471	Yes	0.411
5	0.405	0.460	0.428	0.416	No	—
6	0.398	0.438	0.461	0.515	Yes	0.436

The QTc values above 0.450 are given in bold.

present, previous,¹ and other¹⁶ results show that the mean QTc interval increased after initiation of cisapride treatment, and (c) QTc interval remained prolonged in four infants (nos 1, 2, 4, and 6) and decreased in two of them only when cisapride was discontinued. Another explanation for this transient increase in QTc interval could be maturation of the enzyme system that affects cisapride metabolism. This hypothesis could explain why Levine *et al*¹⁷ reported that verification of the electrocardiogram after one month of treatment with cisapride was always normal, whereas we report an increase in QTc interval in 29% of neonates receiving cisapride for 2–15 days. In any case, if maturation is able to occur quickly, it does not seem to be the case for all infants.

None of the infants in the present study had clinical symptoms related to QTc interval prolongation. Moreover, a recent retrospective survey reported that no deaths attributable to cisapride were reported among > 11 000 pre-term newborns treated.¹⁸ The results of these studies do not imply that there is no risk associated with this cisapride induced increase in QTc because either the population was too small (our study) or the study was retrospective.¹⁸ However, these results raise, but cannot answer, the important following question: what is an abnormal value for QTc interval in the neonatal period?

In conclusion, our data support our initial hypothesis of drug accumulation due to enzyme immaturity. In addition, we have shown that the cisapride induced QTc interval prolongation is also common in term neonates as it went above 0.450 in six (26%) of the neonates included in our survey. Although no clearly established norms for QTc intervals in neonates exist, these intervals are concerning, particularly those of over 0.470 that occurred in two infants. Thus we recommend that QTc interval be determined before and at least 48 hours after initiation of cisapride treatment. If the QTc interval remains below 0.450 but increases between the times of these two measurements, a longer survey is necessary.

Editorial comment

This paper was accepted for publication before the announcement that the Medicines Control

Agency was suspending the product licence for cisapride with effect from 28 July 2000. We decided to go ahead with publication because the UK licence may be reinstated, in which case more information about its effects will be important, and because there may be other parts of the world where cisapride is still being used (on- or off-label) in neonates.

D S S and J-B G are members of the Neonatal Network of Burgundy.

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