Paediatric and Perinatal Drug Therapy, 2006; 7 (2)

Electrocardiographic observations in premature and term infants on cisapride therapy

Charles I Berul[1], Robert M Ward[2], Gregory L Kearns[3], Rene Kerstens[4], Patricia K Robinson[4], Frank A van den Ouweland[4]

[1]*Department of Cardiology, Children's Hospital Boston and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA*

[2]*Department of Neonatology, University of Utah, Salt Lake City, Utah, USA*

[3]*Division of Pediatric Pharmacology and Medical Toxicology, Children's Mercy Hospitals and Clinics, Kansas City, Missouri, USA*

[4]*Johnson & Johnson Pharmaceutical Research and Development LLC, Titusville, New Jersey, USA*

Corresponding author

Frank van den Ouweland, CILAG AG International, Landis & Gyr Strasse 1, CH-6300 Zug, Switzerland.
Email: fouwelan@jnjch.jnj.com

Objective: **An exploratory analysis of the cardiovascular experience of cisapride treatment in premature and term infants with the purpose to advance our knowledge of the effects of Ikr channel modulating compounds in this patient population.**

Methods: **Multi-centre, open-label study including 36 preterm and term neonates up to 6 months of age with gastro-oesophageal regurgitation and at least one additional symptom of neonatal feeding intolerance. On day 1 of the study, the subjects received one single oral dose of 200 microg/kg. Thereafter, cisapride was continued at 200 microg/kg every 6 hours. PK blood samples and ECGs were collected systematically. A single paediatric cardiologist analysed all ECGs in standardised fashion. QT intervals were corrected for heart rate by applying a study-specific correction method (QTcS), and according to Bazett (QTcB), and Fridericia (QTcF).**

Results: **Mean QTcS at baseline was 252 ms; mean QTcB, 396 ms. Statistically significant changes from baseline in QTcS on study days 2–7 varied between +7.9 to +15.6 ms; those for QTcB between +9.8 and +25.9 ms. Incidences of prolonged QTcB occurred at least transiently in seven subjects, but no cardiac arrhythmias were observed. Mean cisapride plasma concentrations on day 4 were C_{+2}: 52 ng/ml, and C_{+6}: 42 ng/ml; and on day 7, C_{+2}: 48 ng/ml, and C_{min}: 40 ng/ml. PK–PD analysis revealed no meaningful relationship between heart rate corrected QT intervals and cisapride plasma concentrations.**

Conclusion: **Overall, changes in QT intervals were judged to constitute no safety concern and to fall within the expected distribution for the study population. The incidental QT prolongations showed no clinically significant relationship with cisapride plasma concentrations, drug exposure or subject age.**

Paed Perinat Drug Ther 2006; 7: 77–88

Keywords: electrocardiography – cisapride – QT intervals – neonates

Introduction

Cisapride, a prokinetic agent, has been extensively investigated in the treatment of gastrointestinal disorders in adult patients. Paediatric expert opinion had endorsed cisapride as the prokinetic drug of choice for feeding intolerance and gastro-oesophageal reflux in neonates and infants[1,2]. In recent years, however, the use of cisapride worldwide has become limited. Concerns around QT interval prolongation and cardiac arrhythmia were discussed among experts. In the vast majority of reported cases of adverse events, patients had risk factors for cardiac rhythm disturbances including the concomitant use of contraindicated medication, depleted serum electrolytes, pre-existing cardiac disease, or other disorders that may predispose to arrhythmia[3,4]. Non clinical research has revealed that cisapride, under certain circumstances, can alter cardiac repolarisation most likely through its effect on the IKr channel[5-7].

We present data from an open-label clinical trial investigating single- and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and cardiac safety of cisapride oral suspension, administered to term and preterm neonates and infants aged 0–6 months. The primary objective of this trial was to characterise the PK of a single oral dose of cisapride[8]. Once the subjects in the trial had completed the primary objective of the study protocol, they could continue with cisapride for a maximum period of 12 weeks (w). The present paper reports on an exploratory objective of the study, specifically to assess the cardiovascular experience of cisapride treatment in premature and term infants. The purpose was to identify any potential associations between cisapride plasma levels and abnormalities in electrocardiographic (ECG) parameters of cardiac conduction and repolarisation, including the QT interval.

Systematically obtained and objectively assessed ECG data from a neonatal study population are notably rare. In this trial, prospectively scheduled ECGs were obtained at baseline before starting cisapride treatment, on several days during cisapride treatment, and at trial termination, using standardised methods. The study findings are particularly important in light of our limited knowledge of the potential effects of IKr channel modulating compounds on cardiac repolarisation in neonates.

Methods

Subjects

Term and premature neonates were eligible for enrolment if they met the following inclusion criteria:

- body weight > 800 g, on continuous cardiac monitoring (for the duration of the study) between the postnatal ages (PNA) of 0–6 months and post-conceptional ages (PCA) of 28-52 w
- regurgitation of oral feedings associated with one or more of the following clinical findings:
  a) an episode of apnoea for > 20 seconds, or of any duration if accompanied by cyanosis, oxygen desaturation or significant bradycardia
  b) clinically significant bradycardia defined in neonates as heart rate <100 min^{-1}, and in infants 1–6 months PNA as <80 min^{-1}
  c) increased gastric residue (>2 ml/kg or >30% of feed) prior to a scheduled feeding, i.e. approximately every 3 hours (h)
- a determination by the attending neonatologist/physician that treatment with cisapride was clinically indicated.

Patients were excluded if any of the following criteria were met:

- a known presence of significant cardiovascular disease
- current respiratory failure
- evidence or history of prolonged QTc intervals, torsade de pointes or other cardiac ventricular arrhythmia
- clinically significant vomiting
- uncorrected electrolyte disturbances such as hypokalaemia or hypomagnesaemia
- a clinically significant disease state with hepatic or renal compromise, systemic hypoperfusion or anaemia
- other abnormal laboratory values
- documented or suspicion of current alcohol or drug abuse in breastfeeding mothers
- receipt of an investigational drug administered as part of a clinical trial within 30 days prior to study enrolment
- recent use (within 14 days before administration of cisapride – for either the subject or mother, if breastfeeding) of a drug or natural product known to inhibit cytochrome P450 isoenzyme 3A4 (CYP3A4), or known to prolong the QT interval
- evidence of a condition and/or surgical procedure that could potentially interfere with drug absorption
- inability to tolerate required study procedures
- known severe drug allergy or hypersensitivity
- planned termination of continuous cardiorespiratory monitoring prior to conclusion of study-related procedures.

Study subjects were enrolled to one the following PCA categories: 28–36 w; 37–42 w; 43–52 w. The PCA was defined as the gestational age plus post-natal age at the time of enrolment into the study. An attempt was made to enrol between 6 and 10 subjects for each PCA category.

Procedures and general assessments

Informed parental consent was obtained before a patient could be enrolled. The study protocol was approved by the institutional review boards or human ethics committees of the participating clinical research institutions (Children's Mercy Hospitals and Clinics, Kansas City, Missouri; Louisiana State University Medical Center, Shreveport, Louisiana; Rainbow Babies and Children's Hospital, Cleveland, Ohio; Children's Hospital and Health Center, San Diego California; University of Utah, Salt Lake City, Utah; and Sophia Children's Hospital, Rotterdam, the Netherlands). The study started in March 1999 and closed in March 2000. All subjects were investigated in a Neonatal Intensive Care Unit (NICU) setting where they were continuously monitored by a specialty nurse and remained throughout the entire observation period. Subjects who no longer required continuous cardiac monitoring in an ICU setting were considered ineligible to continue in the study.

The clinical trial was conducted with active study medication without masking. On day 1, the subjects received one single oral dose of 200 microg/kg cisapride in a 1 mg/ml suspension (Propulsid® Oral Suspension, Janssen Pharmaceutica Inc.). If clinically indicated at the 24 h post dose time point, the subject entered the multiple-dose phase of the study. Cisapride therapy thereafter was continued at 200 microg/kg every 6 h for up to 12 w (days 2 to 84). Preliminary observations supported the dosing schedule with plasma cisapride concentrations in premature neonates in the range of 7–170 ng/ml, similar to those of adults taking 10 mg cisapride tablets 4 times daily[9]. All adverse events with onset on or after the first dose of study drug were recorded, regardless of causality assessment.

ECG recordings and analysis

During screening, a single 12 lead ECG was performed and analysed. After the initial cisapride dose, a six lead (limb leads) ECG was obtained prior to each PK blood sample, immediately pre-dose, and at 0.5, 1, 2, 4, 8, 12, and 24 h after the first dose (on day 1). Thereafter, 6 lead ECGs were obtained on day 2, at 1, 2 and 6 h after the 4th cisapride dose; on day 4, at 1 and 6 h after the 12th cisapride dose; and on day 7, at 1 and 2 h after the 24th cisapride dose. Additionally, 12 lead ECGs were obtained on day 4, at 2 h after the 12th cisapride dose; on day 7, at 6 h after the 24th cisapride dose, and weekly thereafter including a final 12 lead ECG at trial termination. ECGs were recorded at 25 mm per second.

Each ECG recording was sent to a central ECG processing and measurement facility. This central facility managed the ECG data collection and provided the measurements of conduction intervals and derived calculations. The QT intervals were assessed from lead II recordings[10]. If the lead II recording was not adequate to determine the exact duration of the QT interval, a different limb lead recording of the six lead ECG was used. The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as the point at which the downslope crosses the isoelectric baseline. The central ECG facility then sent all original paper recordings to a sponsor-appointed paediatric cardiologist for interpretation and validation. All of the ECG tracings, measurements, and interpretations were coded, blinded for patient identifiers and cisapride dosing. All of the conduction intervals were manually confirmed on original recordings. The paediatric cardiologist's interpretation was sent back to the central facility and from there forwarded on to the clinical trial sites. Only these final data, based on the paediatric cardiologist's interpretation, were used for the study analysis.

QT intervals were corrected for heart rate (QTc) using both the Bazett formula, where $QTcB=QT/(RR^{½})$[11], and the Fridericia formula, $QTcF=QT/(RR^{⅓})$[12]. In addition to the usual applied QT correction formulae, a study-specific correction was developed post-hoc, to analyse the data using a method based on the study sample's own pooled baseline observations of heart rate and QT interval. This study-specific heart rate correction, QTcS, applies a formula with the following structure: $QTcS=QT/(RR/a)^{b}$. The average baseline value of the RR interval over all study subjects determines the value of "a", while the power, "b", is obtained by linear regression on the log transformed QT and RR interval values at baseline. In Figure 1, the baseline QT intervals of the study population are plotted against their corresponding RR intervals; together with the values obtained by the study-specific, Bazett, and Fridericia corrections. In order to determine a cut-off QTcS value characterising a "prolonged" heart rate corrected interval, the equivalent of the upper normal limit of QTcB was applied to QTcS units. The study protocol prospectively defined a heart rate corrected QT threshold of 460 ms; this is based on the neonatal population mean value of QTcB + 3 times the standard deviation

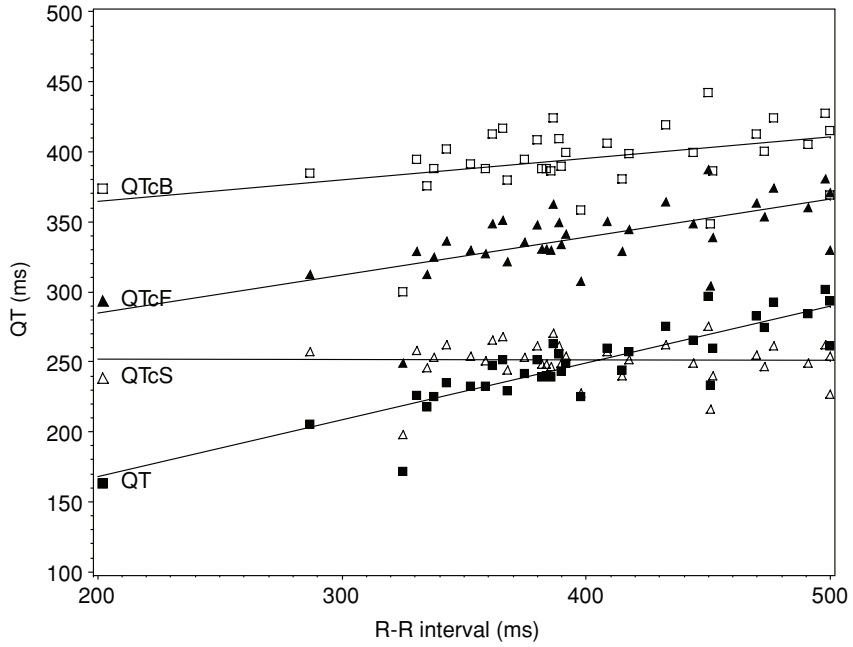

Figure 1 QT intervals and heart rate. The relationship at baseline between the uncorrected QT interval and the R–R interval is demonstrated; assessed from ECG lead II obtained in 35 subjects (QT, ■). The corresponding heart rate corrected QT-intervals, according to Bazett (QTcB, □), Fridericia (QTcF, ▲) and the study-specific correction (QTcS, △) are plotted together. Figure 1 intends to demonstrate QTcS values in relationship with QTcB; QTcS is unaffected by heart rate, but its values are well below those of QTcB. Also, note the under-correction bias in the Fridericia method in the infant population due to the high heart rates.

(SD)[13]. The mean study population baseline QTcS is 252 ms with a SD of 15 ms. The corresponding upper limit for QTcS in this sample, therefore, becomes: mean + 3SD=252+45=297 ms. We were encouraged to construct a study-specific correction by recent developments in regulatory guidance on the evaluation of QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs. In a concept paper by the US FDA, a further exploration and application of regression analysis techniques in controlled clinical trials is advocated[14]. Various other similar methods are reviewed by Malik[15].

Exploratory steady-state pharmacokinetic-pharmacodynamic (PK–PD) investigation

Procedures and handling of PK blood samples as well as the methodology for determination of cisapride in plasma have been described elsewhere[8]. Based on earlier studies, steady state cisapride levels in neonates are achieved, on average, after 48 h of continuous dosing[9]. Therefore day 4 and 7 cisapride plasma concentrations were used together with the QT-intervals of the ECG tracings, recorded prior to each blood sample for an exploratory PK–PD assessment. The objective was to investigate the possible association of changes in heart rate corrected QT interval with cisapride plasma concentrations.

The PK–PD investigations were undertaken in three steps. Each of the subsequent steps intends to reduce the inherent inter- and intra-subject variability in cisapride concentrations, as well as in the corrected QT intervals. The first step was an evaluation of the correlation between plasma cisapride concentrations versus QTc; the second step correlated plasma cisapride concentrations versus changes from baseline in QTc intervals; and in the third step, a measure of cisapride exposure defined by an inter-dose concentration versus time area under curve (AUC) calculated from the plasma cisapride concentrations at 2 h and at 6 h post dose, was correlated with differences in the QTc for these two time points. Each step was evaluated by linear regression analysis. Statistical analyses for each regression included assessment of the correlation coefficient (r^2), and whether the slope of the regression line was different from zero.

Finally, occurrences of prolonged QTc as defined prospectively in the study protocol, i.e. all subjects experiencing one or more events of QTcB and QTcF intervals greater than 460 ms on ECG, and any changes from baseline in these variables greater than 60 ms, were reviewed in detail. Correspondingly, post-hoc, all occurrences of QTcS greater than 297 ms, or changes from baseline QTcS exceeding +45 ms were included in the review. For each of the subjects with data meeting these criteria, an individual assessment

of all available cisapride exposure data (inferred from blood samples taken on days 1, 2, 4, 7, as well as subsequent plasma cisapride determinations) was performed.

Results

Subject demographics

Thirty six neonates and young infants (age range 28–54 w PCA) were enrolled. One patient unintentionally received an incorrect single dose of cisapride (100 microg/kg) and was excluded from analyses. There were no safety-related concerns in this study subject. Demographic details of the 35 subjects included in the study are presented by PCA category in Table 1.

Subject disposition

Six subjects received a single dose of cisapride on day 1 only: three discontinued because of a lack of vascular access, two because of adverse events and one became ineligible to continue the study. Of the 29 subjects who entered the multiple dose phase, no subject participated for the entire allowed period of 12 treatment weeks. Median and range of cisapride therapy duration is displayed in Table 1. The most common reason for discontinuation, for 20 (56%) subjects, was the development of ineligibility for continued participation (e.g. hospital discharge or removal of continuous cardiac monitoring when no longer clinically indicated). Of the enrolled subjects who remained on cardiac monitors, three subjects ended the study early in connection with adverse experiences, three were withdrawn due to insufficient therapeutic response, three were considered no longer in need of cisapride therapy and the remaining seven discontinued for various reasons. Subject disposition relative to ECG observation time points is indicated in the results tables.

Cisapride plasma concentrations

Table 2 presents the 2 h cisapride plasma concentration, C_{+2}, and 6 h post dose, C_{+6}, values on days 4 and 7 of cisapride treatment by PCA category. The differences between plasma cisapride C_{+2} and the corresponding C_{+6} values on day 4 and day 7 are not statistically significant for each of the PCA categories. The mean cisapride plasma levels on both days were highest in the 28-36 w PCA group; however, differences between the mean values of the 28-36 and >37-42 w PCA categories are not statistically significant and the concentration ranges show considerable overlap. In the oldest PCA category, the number of subjects with data was too small to make a comparison meaningful.

ECG results

Baseline ECG data

Baseline ECG parameters by PCA group are displayed in Table 3. Mean baseline heart rate was the highest, hence mean RR interval the shortest, in the youngest PCA group. Corresponding with the higher heart rate, the uncorrected mean QT interval, 237 (SEM 6.5) ms, in the 28–36 w PCA category was shorter than that of the 2 older PCA groups: 265 (6.0) and 260 (11.6) ms, respectively. Also, mean baseline QRS interval of the youngest PCA group was shorter, 50 (2.3) ms, than that of the two older PCA groups: 58 (2.1) ms and 62 (0.8) ms, respectively. As expected, after correction for heart rate, the difference in QT interval between PCA groups disappears. Both the Bazett and Fridericia correction methods relate the observed QT interval to a QT at a "normal" heart rate of 60 min^{-1}. Mean baseline values of QTcB, 396 (4.3) ms, and QTcF, 340 (4.3) ms, therefore, are expected to be higher than the values for QTcS, the study-specific correction of the QT interval that applies pooled baseline data from all study subjects to adjust for heart rate. The mean baseline QTcS is 252 (2.6) ms (Figure 1).

Table 1 Clinical characteristics of the infants and duration of cisapride therapy

	PCA (w)			
Parameter	**28–36**	**37–42**	**43–54**	**Total**
Total number of subjects treated	17	13	5	35
Male	11	7	4	22
Caucasian	10	9	2	21
Postnatal age (days)				
Median	29	30	75	37
Range	4–67	6–88	47–102	4–102
Gestational age (w)				
≤ 36	17	8	0	25
> 36	0	5	5	10
Median	29	36	40	31
Range	26–32	26–40	38–41	26–41
Weight (kg)				
Median	1.7	3.1	4.0	2.2
Range	1.0–2.6	1.7–4.8	3.2–6.6	1.0–6.6
Cisapride treatment duration (days)				
Median	10	7	5	8
Range	1–39	1–24	2–13	1–39

Table 2 Cisapride plasma concentrations at steady state

	PCA (w)			
Cisapride plasma concentration (ng/ml)	**28–36**	**37–42**	**43–54**	**Total**
Day 4, at 2 h post dose (C_{+2})				
n	13	8	3	24
Mean	58	51	29	52
SEM	9.6	12.1	8.6	6.7
Range	13–121	9–98	14–43	9–121
Day 4, at 6 h post dose (C_{+6})				
n	13	8	3	24
Mean	47	41	23	42
SEM	7.2	12.1	9.1	5.8
Range	11–92	8–113	12–41	8–113
Day 7, at 2 h post dose (C_{+2})				
n	10	7	1	18
Mean	54	45	9	48
SEM	14.7	9.4	–	9.0
Range	7–128	6–81	–	6–128
Day 7, at 6 h post dose (C_{+6})				
n	9	6	1	16
Mean	38	47	6	40
SEM	11.6	9.3	–	7.6
Range	5–97	14–83	–	5–97

Heart rate changes

Overall changes from baseline in mean heart rate tended toward a decrease during the course of the trial. On days 2–7 the mean (SEM) decrease in heart rate varied between a minimum change of –1.3 (4.49) min^{-1} on day 7, at 1 h post dose to a maximum change of –7.3 (4.70) min^{-1} on day 2, at 2 h post dose. On the ECG taken around the time of presumed peak plasma cisapride concentrations, 2 h post dose, the change from baseline heart rate of 152 min^{-1}, on day 2 was -7.3 (4.70) min^{-1}, on day 4, it was -6.4 (4.34) min^{-1}, and on day 7, the change was –2.9 (3.71) min^{-1}. The decrease in heart rate was most pronounced and, based on 95% confidence interval limits, statistically significant from baseline at several time points during days 2–7 in the 28–36 w PCA group.

Heart rate corrected QT interval changes

Mean changes from baseline and corresponding 95% confidence intervals for the heart rate corrected QT intervals are presented for each time point in Table 4. Overall, changes from baseline in the mean uncorrected QT interval showed an increase during days 2–7 of the trial, consistent with the decrease in heart rate. Among the three different PCA categories, the uncorrected QT interval changed significantly from baseline only in the 28–36 w PCA group on days 2–7 of cisapride administration. The maximum mean (SEM) change from baseline of uncorrected QT in the 28-36 w PCA group was +28 (6.0) ms, on day 4 at 6 h post dose. No significant changes in the mean QT interval were observed in the two older PCA groups.

QTcB, QTcF and QTcS increased statistically significantly at various time points on day 1. On days 2–7, further statistically significant increases in QTcB , QTcF and QTcS occurred (Table 4). However, the time points of significant increases in QTcS do not reveal a consistent pattern, nor do they coincide with the average peak cisapride plasma C_{+2}, at 2 h post dose. The frequency of significant mean changes from baseline QTc value (by all 3 methods of heart rate correction), as well as the magnitude of change are similar across the three PCA categories. The highest values for mean change in QTcB and QTcF on day 1 are +7.5 (3.0) at 4 h post dose and +6.3 (2.9) ms at 2 h post dose; the largest change in QTcS on day 1 is 5.1 (2.1) at 4 h post dose. The statistically significant changes from baseline in QTcS on days 2–7 vary

Table 3 Baseline ECG parameters

	PCA (w)							
Parameter	**28–36**		**37–42**		**43–54**		**Total**	
(Intervals in ms)	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Uncorrected QT interval	237	6.5	265	6.0	260	11.6	251	4.7
QTc Bazett	389	7.0	405	4.8	397	12.7	396	4.3
QTc Fridericia	330	6.7	352	4.8	345	11.7	340	4.3
QTcS (study-specific)	250	4.1	255	3.3	250	8.5	252	2.6
Heart rate (min^{-1})	163	4.6	142	5.2	142	9.1	152	3.6
R–R interval	374	10.4	431	15.7	447	28.7	403	9.6
PR interval	100	2.7	98	3.8	102	7.2	99	2.1
QRS interval	50	2.3	58	2.1	62	0.8	55	1.6
JT interval	187	6.7	207	5.4	197	11.9	196	4.4

Table 4 Changes in ECG parameters following treatment

Day & time relative to dose		*n*	uncorrected QT Baseline: 251 ms		QTcB Baseline: 396 ms		QTcF Baseline: 340 ms		QTcS Baseline: 252 ms	
			Mean change	95% confidence interval	Mean change	95% confidence interval	Mean change	95% confidence interval	Mean change	95% confidence interval
Day 1	+ 0.5h	35	0.9	–6.4 to 8.1	0.1	–5.1 to 5.2	0.3	–5.0 to 5.7	-0.1	–4.0 to 3.8
	+ 1h	35	4.5	–3.9 to 12.0	7.5	0.1 to 15.0	6.1	-0.8 to 13.1	5.0	–0.0 to 10.0
	+ 2h	35	6.3	–1.2 to 13.7	6.4	0.6 to 12.1	6.3	0.4 to 12.3	3.2	–0.7 to 7.1
	+ 4h	35	3.9	–2.3 to 10.0	7.5	1.3 to 13.6	6.1	0.3 to 11.8	5.1	0.92 to 9.3
	+ 8h	35	0.9	–5.6 to 7.5	5.6	–0.9 to 12.2	3.5	–2.6 to 9.7	4.4	0.2 to 8.7
	+ 12h	34	1.3	–5.9 to 8.4	1.6	–5.8 to 9.0	1.4	–5.6 to 8.5	0.9	–3.8 to 5.7
	+ 24h	35	5.0	–4.0 to 14.0	6.6	–0.16 to 13.3	5.9	–1.6 to 13.3	4.0	0.11 to 7.9
Day 2	+ 1h	29	8.1	–2.2 to 18.4	8.9	–0.4 to 18.2	8.7	–0.2 to 17.6	4.8	–1.4 to 11.0
	+ 2h	26	15.6	3.3 to 27.9	16.5	5.2 to 27.7	16.4	5.2 to 27.5	8.8	1.9 to 15.7
	+ 6h	28	14.3	4.2 to 24.3	17.0	7.4 to 26.6	16.0	6.8 to 25.3	9.6	3.5 to 15.8
Day 4	+ 1h	25	9.8	0.5 to 19.2	13.3	2.6 to 24.0	12.0	2.3 to 21.7	7.9	1.1 to 14.8
	+ 2h	24	10.3	–0.4 to 21.0	9.8	0.4 to 19.3	10.3	0.5 to 20.1	4.7	–0.9 to 10.4
	+ 6h	26	16.6	7.1 to 26.1	20.6	9.0 to 32.3	19.3	8.9 to 29.8	11.7	4.2 to 19.2
Day 7	+ 1h	17	6.2	–5.5 to 18.0	7.2	–4.8 to 19.2	6.8	–4.4 to 18.1	3.9	–3.9 to 11.7
	+ 2h	18	18.4	7.1 to 29.7	25.9	15.8 to 36.0	23.1	12.7 to 33.4	15.6	9.6 to 21.6
	+ 6h	21	5.4	–5.3 to 16.1	3.9	–3.7 to 11.4	4.5	–3.8 to 12.9	1.2	–3.5 to 5.9

between a mean change of +7.9 (3.3) to +15.6 (2.8) ms; those for QTcB vary between +9.8 (4.6) ms and +25.9 (4.8) ms; and for QTcF between +10.3 (4.7) ms and +23.1 (4.9) ms. Looking at each of the PCA categories, statistically significant changes from baseline in the corrected QT are observed for each of the PCA groups for QTcB and QTcS, again, at various time points during days 2–7. However, these time points do not show a consistent pattern, nor do they coincide with the average peak cisapride plasma concentrations at around 2 h post dose. The frequency of statistically significant mean changes from baseline in the heart rate corrected QT intervals, as well as their magnitude, are similar across the 3 PCA categories. After day 7, the number of subjects with data is too small to make meaningful inferences.

Taking all of these data together, the mean changes in QTc (using any of the three methods of heart rate correction) were not considered clinically unsafe. The highest mean QTcB observed was 417 (7.9) ms on day 7 at 1.45 h post dose, corresponding to the highest mean QTcF of 359 (7.7) ms at the same time point. Individual subjects' changes in QTcB or QTcF of more than +60 ms from baseline (QTcS, over 45 ms), or occurrences of QTcB or QTcF values over 460 ms (QTcS over 297 ms) are discussed in the section describing adverse events. No apparent differences by sex were observed in change from baseline QTc intervals; however, there were a small number of female subjects (10 or less) from day 2 onward, making a meaningful comparison difficult.

PK-PD: effect on the QT interval during steady state

The relation of steady-state plasma cisapride concentrations to corrected QT intervals was undertaken in three steps, each using data obtained at 2 h and 6 h after the 12th dose on day 4, and 2 and 6 h after the 24th cisapride dose on day 7 of treatment. The first step investigated the correlation of the absolute plasma cisapride concentrations C_{+6} at 6 h post dose, and C_{+2}, at 2 h post dose, with QTcB and QTcS, respectively. Because the QTcF interval values parallel those of QTcB, this parameter was left out of the PK–PD analysis. Most subjects experience a relatively small change in cisapride plasma concentration going from the generally higher values at 2 h post dose to the values at 6 h post dose; however not all subjects follow this pattern and there is marked individual variation (Figure 2a). Even in those with a large change in cisapride concentration, the relationships with change in QTcB are not particularly striking. The regression equations are provided in Figure 2, and the regression lines are drawn in for the values of C_{+6} (dashed line) and C_{+2} (a solid line). While the slopes of the regression lines are statistically significant for both C_{+6} and C_{+2} values on day 4, the explained variance is small (r^2 value of 0.175 for C_{+2}) and, counter to expectation, r^2 is slightly larger at the 6 h cisapride plasma C_{+6} concentration: 0.289. Day 7 observations show a very similar picture, however, the regression analysis is not statistically significant. Table 5 summarises the correlation characteristics for QTcB and QTcS on days 4 and 7. In the second step of the PK-PD analysis, day 4 cisapride plasma concentrations are correlated with the change from baseline in QTcB and QTcS, respectively. Neither correlation shows a significant relationship (Figure 2b). Nor did the third step, associating days 4 and 7 cisapride exposure by means of an interdose AUC with the changes in QTcB and QTcS between C_{+6} and C_{+2} show a significant relationship (Table 5).

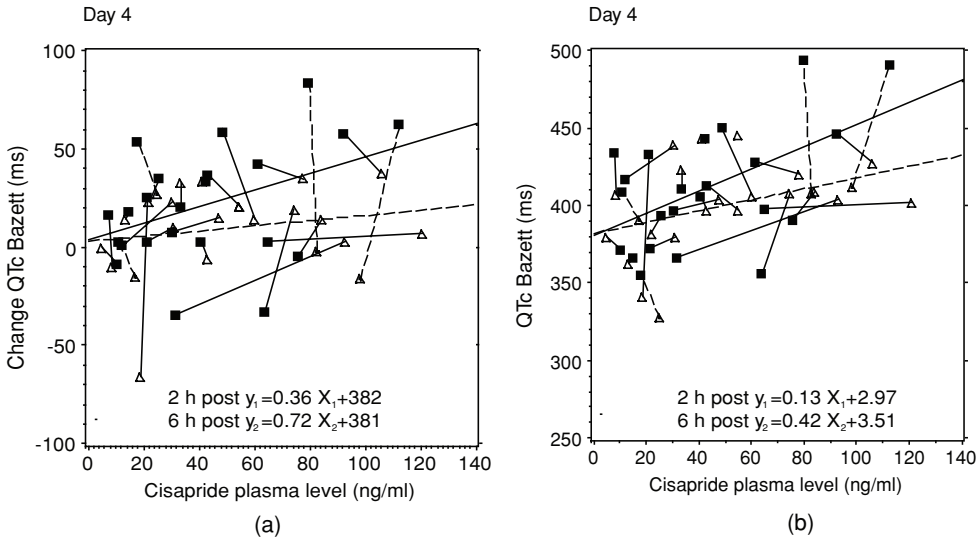

Figure 2 Cisapride concentrations versus QTcB and change from baseline QTcB, on day 4. In panel a the individual subject cisapride plasma concentrations at 2 h (C+*2*, Δ) and 6 h post dose (C+*6*, ■) are plotted versus heart-rate corrected QT-interval according to Bazett, QTcB. The paired observations for 24 subjects on day 4 are each connected by a line. The overall correlation between cisapride plasma concentration, in ng/ml on the abscissa, and QTcB, in milliseconds on the ordinate, for the values at 2 h post dose (C+*2*, solid line) and at 6 h post dose (C+*6*, dashed line) are shown in panel a, together with the regression equations. In panel b the cisapride individual subject plasma concentrations at 2 h (C+*2*, Δ) and 6 h post dose (C+*6*, ■) are plotted versus the change from baseline in QTcB. Paired observations are each connected by a line. The overall correlation between cisapride concentration and change in QTcB for the values at 2 h post dose (C+*2*, solid line) and 6 h post dose (C+*6*, dashed line), together with the regression equations are shown in panel b. Four of seven subjects described in Table 6 for which day 4 data were available have been indicated by dashed lines.

Summary of individual QT prolongation incidents and reported adverse events

No ventricular arrhythmias or deaths were reported. Three subjects were recorded by the investigator with an incident of "prolonged QT" (Table 6, subjects E, F and G). None of these events was considered serious by the clinicians caring for the subjects, or caused overt clinical symptoms. Four other subjects (Table 6, subjects A, B, C, D) had one or more incidents of heart rate corrected QT prolongation on the ECG tracings as defined per protocol (i.e. either QTcB or QTcF more than 460 ms, or a QTcB and/or QTcF increase of more than 60 ms from baseline value).

For each of these seven subjects, an assessment was made of cisapride exposure relative to the distribution of corresponding values for all study subjects. Cisapride exposure was expressed as plasma concentration AUC after the first dose until last measurement on day 1, and the AUC over the time and concentration course between 2 and 6 h after 12th cisapride dose on day 4. Only one of the three investigator-reported cases and one of the four subjects with protocol-defined events of QTc prolongation had cisapride exposure, expressed as AUC, values in the upper half of the study population distribution. In all six other cases, the plasma cisapride exposure value was average or low, relative to the population distribution of AUC values.

Adverse events, meaning any untoward medical occurrence during the course of the study regardless of a possible relationship with treatment, were reported for 80% of subjects. The most common adverse events (four subjects

Table 5 Correlation between plasma concentrations of cisapride and heart rate corrected intervals

	Day 4 of cisapride treatment				Day 7 of cisapride treatment			
Plasma concentration and corrected QT interval	***n***	***r*²**	**Slope**	**95% confidence interval slope**	***n***	***r*²**	**Slope**	**95% confidence interval slope**
C_{+2} versus QTcB	24	0.1753	0.3587	0.0146 to 0.7028	17	0.0236	0.1385	–0.3520 to 0.6289
C_{+6} versus QTcB	23	0.2890	0.7191	0.2073 to 1.2309	14	0.0028	–0.0268	–0.3422 to 0.2887
C_{+2} versus change QTcB	24	0.0388	0.1322	–0.1588 to 0.4231	17	0.0116	0.0587	–0.2395 to 0.3569
C_{+6} versus change QTcB	23	0.1640	0.4248	–0.0104 to 0.8599	14	0.0052	0.0346	–0.2663 to 0.3354
$AUC_{2\text{-}6}$ versus d-QTcB	22	0.0080	0.0281	–0.1180 to 0.1740	14	0.0008	–0.0047	–0.1108 to 0.1015
C_{+2} versus QTcS	24	0.2564	0.2811	0.0694 to 0.4928	17	0.0588	0.1246	–0.1498 to 0.3990
C_{+6} versus QTcS	23	0.3403	0.4966	0.1828 to 0.8104	14	0.0050	0.0203	–0.1590 to 0.1996
C_{+2} versus change QTcS	24	0.0847	0.1164	–0.0528 to 0.2856	17	0.0136	0.0377	–0.1390 to 0.2145
C_{+6} versus change QTcS	23	0.1685	0.2781	–0.0023 to 0.5585	14	0.0006	–0.0065	–0.1734 to 0.1604
$AUC_{2\text{-}6}$ versus d-QTcS	22	0.0056	0.0147	–0.0763 to 0.1056	14	0.0040	–0.0058	–0.0633 to 0.0518

Table 6 Clinical details of patients experiencing QTc prolongation

Subject	PCA (w)	PNA (days)	Weight (kg)	Occurrence of event	QTcB (msec)	QTcB increase from baseline (ms)	Cisapride plasma concentration (ng/ml)	Day 1 AUC_{last} (ng x h/ml)	Day 4 AUC_{2-6} (ng x h/ml)
A	28	14	0.98	Day 2, +2 h	390	89	12	153	86
				Day 2, +6 h	391	90	19		
				Day 4, +1 h	367	66	34		
B	35	48	2.21	Day 1, +24 h	468	58	15	629	310
				Day 2, +1 h	465	55	46		
				Day 2, +6 h	478	68	60		
				Day 4, +1 h	480	70	95		
				Day 4, +6 h	494	84	80		
				Day 7, +1 h	462	52	63		
				Day 7, +2 h	487	77	66		
C	36	53	2.11	Day 1, +24 h	468	25	9	406	no data
				Day 2, +2 h	461	18	42		
D	37	13	2.81	Day 1, +1 h	465	59	10	128	57
E	39	12	3.87	Day 3	No data		No data	567	417
				Day 4, +6 h	491	63	113		
				Day 5	No data		No data		
F	39	62	3.13	Day 1, +1 h	445	20	10	196	no data
G	51	88	5.48	Day 1, +2 h	474	54	40	312	no data

each) were heart murmur, rash, sepsis, and urinary tract infection. With the exception of the three events of QT prolongation, the clinical investigators considered all adverse events to be unrelated to cisapride. Two subjects (both PCA 28-36 w) experienced serious adverse events, considered unrelated to cisapride and both subjects recovered. In total, three subjects discontinued the trial because of adverse experiences: one because of enterococcus septicaemia on day 1; one because of a feeding disorder on day 11, not related to study drug; one was discontinued after the 1st dose, because of a suspected QT prolongation on day 1. However, each of the validated corrected QT interval measurements for this subject was within the normal limits (longest QTcB observed was 445 ms at 1 h post dose).

Discussion

Cisapride was well tolerated by the preterm and term infant patients in this study. There were no episodes of ventricular arrhythmias, sudden cardiac death, or excessive QT prolongation. The changes in QT and heart rate corrected QT intervals observed in this study, in absolute values as well as in relation to their individual baselines, are in range of the known intra-subject variability. The heart rate and QT intervals in neonates have marked variability, particularly in the first days of life. In a permanent ECG monitoring study[16] of 29 normal newborns between 1 and 6 days PNA and gestational age of 38–43 w, the overall average heart rate was 130 min^{-1}. The overall average QTcB interval from lead II was (mean ± SD) 405±27 ms; and the variation in individual QTcB intervals was 97 ± 28 ms with a range of 52 to 160 ms[16]. Data from a newborn population survey revealed a mean ± SD QTcB at 4 days of age in normal infants to be 397±18 ms (n=3,946)[17]. The QTcB during the first weeks of life develops to a longer interval with a mean duration of 409±15 ms at 2 months (n=2,418; $P<0.0001$), after which the QTcB returns to 400±14 ms by 6 months of life[17]. The average QTcB values in neonates and their temporal trend to prolongation during the first weeks were confirmed by another paediatric ECG study, which in addition, found no differences in QTcB according to sex or race[18].

On first assessment of the present data, the conclusion must be that the changes in QT and heart rate corrected QT fall within the spectrum of the expected, normal distribution for these ECG parameters in neonates, including presence of the occasional outlier value. Independent from pharmacological intervention, temporal changes in QTcB of neonates between 0 and 6 months of age have been described. Because this study did not include a placebo group, we are unable to correct for or distinguish any potential treatment-related changes in heart rate or QT intervals from the age-related trends in these parameters.

The duration of the QT interval has an inverse relationship to heart rate and the commonly applied method to assess QT corrected for heart rate is that of Bazett[11,13]. Apart from its ubiquity, the Bazett formula has the advantage of simplicity but when heart rate is high, as in the neonatal and infant population under study, it may produce over-correction[19-21]. The opposite consideration, i.e. an under-correction at a high heart rate, applies to the Fridericia method[19-20]. The graphical representation of R–R versus the corrected QT intervals in Figure 1 demonstrates the under-correction by the Fridericia method. Bazett's correction appears acceptable for this study population, given its mean and distribution of individual QTcB values at baseline, as well as the near horizontal plane through which the regression line extends over the infants' heart rate range. While this runs counter to the experience

of over-correction expected for QTcB, this perception is framed by presentations of Bazett's correction applied to QT intervals in adults. Figure 1 illustrates the absence of correction bias by the study-specific correction, as QTcS is based on the actual observed data sample, thus providing an optimised pooled heart rate correction. The study-specific correction, however, is much lower than the familiar range of QTcB values and does not have a recognisable clinical reference.

Our study confirmed the absence of a clinically meaningful relationship between cisapride plasma concentrations and heart rate corrected QT intervals. The review of individual cisapride exposure in subjects with prolonged rate corrected QT intervals revealed coinciding high plasma cisapride levels in only two of the seven subjects. The incidents of changes from baseline of over 60 ms in QTcB (or 45 ms for QTcS) seem associated with spuriously low baseline values, and were not particularly informative with respect to arrhythmia risk. The time points when higher cisapride plasma concentrations were observed were not convincingly associated with increments from baseline or high absolute values of QTcB or QTcS, either by individual subject assessment, or in the stepwise PK–PD analysis. There are changes from baseline in corrected QT intervals in some subjects on day 1 of cisapride exposure, at still relatively low plasma concentrations. On continued treatment, occasional incidents of prolonged QT interval occurred, but clustered in a few subjects. The frequency of QTc prolongation events was not related to subject age. We conclude there is no simple cause-and-effect relationship explaining the incidental changes in corrected QT intervals. The relationship of cisapride dose and effect on conduction characteristics of myocardial tissue is complex, as demonstrated by a recently published non clinical study revealing an inverse relationship between cisapride dose and ventricular arrhythmia vulnerability[22]. The findings of our clinical study, however, are consistent with other documented observations in neonates[20,23].

Whether exceeding a QTcB threshold of 460 ms has clinical relevance in terms of increased arrhythmia vulnerability has not been established; this study only confirms the absence of events in a relatively small sample. In a recent publication, Chhina et al. reported cardiac safety results of a prospective cohort study with 50 neonates who received 800 microg/kg cisapride per day[24]. In 15 subjects, a QTcB value ≥450 ms was observed at some point during cisapride treatment; nevertheless, in 10 of the 15 subjects cisapride was continued uninterrupted. No untoward cardiac arrhythmia or cisapride-related adverse events were reported. Reviews suggest that in neonates, QTcB values over 500 ms are associated with symptoms and QTcB values over 600 ms correlate with severe arrhythmias[13,25,26].

QTcS possibly has higher specificity than QTcB to identify heart rate independent changes, particularly germane in the neonatal and infant population with an innate high and variable heart rate. Should more pre-dose ECGs for each of the study subjects have been obtained and reviewed with similar systematic methodology, more robust estimates of the individual baseline ECG parameters and their variability may have been established, leading to subject specific correction methods[15,21]. For the purpose of inter- and intra-group comparisons in randomised controlled clinical trials, the study- and subject-specific heart rate correction methods deserve more recognition. In contrast, the QTcF correction formula results in too much under-correction and, therefore, its merit for use in the neonatal and infant population is limited. Although measurement and standardisation techniques capable of demonstrating small differences in QT interval were recently developed, the predictive value of minor changes in QTc, using individual or pooled heart rate correction, for risk of cardiac arrhythmia in an individual subject, remain undetermined[27], particularly in infants where fewer well-documented studies are available.

Apart from body weight, which is taken into account in the recommended dosing regimen, no specific characteristics to identify subgroups at risk were identified in this, and two earlier single- and one multiple-dose PK-PD studies in neonates[8,28,29]. This inference does not exclude that, at higher than recommended doses, or when cisapride metabolism is blocked by concomitant administration of a potent CYP3A4 inhibitor, a dose- or concentration-related effect on cardiac repolarisation could be present as some findings in paediatric patients suggest[30-32]. In clinical ECG studies in adults, a relationship between QT prolongation and cisapride plasma concentration has been confirmed only when cisapride is administered in supra-therapeutic doses or in combination with a potent CYP3A4 inhibitor[33,34]. In the present study, days 4 and 7 cisapride plasma concentrations showed a wide range of values similar to earlier observations[9]. Incomplete and delayed absorption of study drug due to the implications of reflux disease in the population of infants in this study, most likely, have contributed to the variability in cisapride plasma levels. A second plausible cause, particularly of relevance in preterm infants, is the developmental dependence of cisapride metabolism. In adults, cisapride is extensively metabolised

in the liver to norcisapride via N-dealkylation (41-45% of the administered dose) and several minor metabolites[35], primarily by CYP3A4[36,37]. Developmental differences in enzyme capacity or activity would have an effect on both bioavailability and total body clearance of cisapride in neonates. CYP3A4 activity at one month of age appears to be only 30–40% of the adult activity[38]. Hepatic microsomes from fetuses and neonates less than seven days old have little ability to catalyse the biotransformation of cisapride, consequent to low CYP3A4 activity[39]. The results of the primary objective of our study confirmed that cisapride absorption and metabolism are developmentally dependent and total body clearance in neonates is reduced when compared to data from older children and adults[8]. The cisapride steady state plasma concentrations by PCA category (Table 2) are consistent with the notion of a developmental dependence of cisapride whole body clearance in neonates.

Limitations

Because this study did not include a placebo treatment group, potential treatment-related changes in heart rate corrected QT interval can not be corrected for the age-related trends in neonatal QTc as described in the literature. Subgroup analyses are limited by a relatively small number of study subjects, particularly the sample of 43–54 w PCA subjects; therefore inferences between age groups have modest power.

Conclusions

The changes in QT and heart rate corrected QT intervals observed in this study fall within the spectrum of the expected, normal distribution for these ECG parameters in neonates. In some subjects, modest and sporadic increases in the heart rate corrected QT intervals were observed, after the first dose as well as during the continuous administration phase of the study, but these events showed no clinically significant relationships with cisapride plasma concentration, drug exposure, or subject age.

References

1. Vandenplas Y, Belli DC, Benatar A et al. The role of cisapride in the treatment of pediatric gastroesophageal reflux. A medical position statement of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 1999;28:518-528
2. Schulman RJ, Boyle JT, Coletti RB et al. The use of cisapride in children. A medical position statement of the North American Society for Pediatric Gastroenterolgy and Nutrition. J Pediatr Gastroenterol Nutr 1999;28:529-533
3. Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001;96:1698-1703
4. Barbey JT, Lazzara R, Zipes DP. Spontaneous adverse event reports of serious ventricular arrhythmias, QT prolongation, syncope and sudden death in patients treated with cisapride. J Cardiovasc Pharmacol Ther 2002;7:65-76
5. Carlsson L, Amos GJ, Andersson B et al. Electrophysiological characterization of the prokinetic agents cisapride and mosapride in-vivo and in-vitro: implications for proarrhythmic potential? J Pharmacol Exp Ther 1997;282:220-227
6. Mohammad S, Zhou Z, Gong Q, January CT. Blockage of the HERG human cardiac K+ channel by the gastrointestinal prokinetic agent cisapride. Am J Physiol 1997;273 (Heart Circ Physiol 42): H2534-2538
7. Drolet B, Khalifa M, Daleau P, Hamelin BA, Turgeon J. Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation 1998;97:204-210
8. Kearns GL, Robinson PK, Wilson JT et al. Cisapride disposition in neonates and infants: In vivo reflection of cytochrome P450 3A4 ontogeny. Clin Pharmacol Ther 2003;74:312-325
9. Janssen Research Foundation, Beerse, Belgium. Data on file
10. Azie NE, Adams G, Darpo B et al. Comparing methods for detecting drug-induced changes in the QT interval: implications for thoroughly conducted ECG studies. Ann Noninv Electrocardiol 2004;9:166-174
11. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353-370
12. Fridericia LS. Die systolendauer im elektrocardiogramm bei normalen menschen und bei herzkranken. Part I. Beziehung zwischen der pulsfrquenz und der dauer des ventrikelelektrokardiogramms bei normalen menschen in der ruhe. Acta Med Scand 1920;53:469-486. [An English translation is available: The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. Part I. Relationship of the pulse frequency (heart rate) and the duration of the ventricular electrocardiogram (QT interval) in normal humans at rest. Translated from German by G Beutner. Ann Noninvasive Electrocardiol 2003;8:343-351]
13. Schwartz PJ, Garson A, Paul T et al. Guidelines for the interpretation of the neonatal echocardiogram. Eur Heart J 2002;23:1329-1344
14. Food and Drug Administration, Nov 15. 2002. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Preliminary Concept Paper (for discussion purposes only). http://www.fda.gov/cder/calendar/meeting/qt4jam.pdf
15. Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol 2001;12:411-420
16. Montague TJ, Taylor PG, Stockton R, Roy DL, Smith ER. The spectrum of cardiac rate and rhythm in normal newborns. Ped Cardiol 1982;2:33-38
17. Schwartz PJ, Montemerlo M, Facchini M et al. The QT interval throughout the first 6 months of life: a prospective study. Circulation 1982;66:496-501

18. Schaffer MS, Trippel DL, Buckles DS, et al. The longitudinal time course of QTc in early infancy. Preliminary results of a prospective sudden infant death syndrome surveillance program. J Perinatol 1991;11:57-62
19. Benatar A, Decraene T. Comparison of formulae for heart rate correction of QT interval in exercise ECGs from healthy children. Heart 2001;86:199-202
20. Benatar A, Ramet J, Decraene T, Vandenplas Y. QT interval in normal infants during sleep with concurrent evaluation of QT correction formulae. Med Sci Monit 2002;8:CR351-356
21. Shah A, Hajian G. A maximum likelihood approach for estimating the QT correction factor using mixed effects model. Statist Med 2003;22:1901-1909
22. DiDiego JM, Belardinelli L, Antzelevitch C. Cisapride-induced transmural dispersion of repolarization and torsade de pointes in the canine left ventricular wedge preparation during epicardial stimulation. Circulation 2003;108:1027-1033.
23. Zamora SA, Belli DC, Friedli B, Jaeggi E. 24-hour electrocardiogram before and during cisapride treatment in neonates and infants. Biol Neonate 2004;85:229-236
24. Chhina S, Peverini RL, Deming DD et al. QTc interval in infants receiving cisapride. J Perinatol 2002;22: 144-148
25. Villain E, Levy M, Kachaner J, Garson A. Prolonged QT interval in neonates:benign, transient, or prolonged risk of sudden death. Am Heart J 1992;124:194-197
26. Garson A, Dick M, Fournier A et al. The long QT syndrome in children. An international study of 287 patients. Circulation 1993;87:1866-1872
27. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-1032
28. Preechagoon Y, Charles B, Piotrovskij V, Donovan T, Van Peer A. Population pharmacokinetics of enterally administered cisapride in young infants with gastro-oesophageal reflux disease. Br J Clin Pharmacol 1999;48:688-693
29. Odoul F, Le Guellec C, Henrot A et al. Population pharmacokinetics of cisapride in neonates. Eur J Clin Pharmacol 2002;58:507-513
30. Hill SL, Evangelista JK, Pizzi AM, Mobasseleh M et al. Proarrhythmia associated with cisapride in children. Pediatrics 1998;101:1053-1056
31. Khongphatthanayothin A, Lane J, Thomas D et al. Effects of cisapride on QT interval in children. J Pediatr 1998;133:51-56
32. Ward RM, Lemons JA, Molteni RA. Cisapride: a survey of the frequency of use and adverse events in premature newborns. Pediatrics 1999;103:469-472
33. van Haarst AD, van 't Klooster GAE, van Gerven JMA et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clin Pharmacol Ther 1998;64:542-546
34. Janssen Research Foundation, Beerse, Belgium. Data on file
35. Meuldermans W, Van Peer A, Hendrickx J et al. Excretion and biotransformation of cisapride in dogs and humans after oral administration. Drug Metab Dispos 1998;16:403-409
36. Bohets H, Lavrijsen K, Hendrickx J et al. Identification of the cytochrome P450 enzymes involved in the metabolism of cisapride: in vitro studies of potential co-medication interactions. Br J Pharmacol 2000;129:1655-1667
37. Pearce RE, Gotschall R, Kearns GL, Leeder JS. Cytochrome P450 involvement in the biotransformation of cisapride and racemic norcisapride in vitro: differential activity of individual human CYP3A isoforms. Drug Metab Dispos 2001;29:1548-1554
38. Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T. Expression of CYP3A in human liver. Evidence that the shift between CYP3A47 and CYP3A4 occurs immediately after birth. Eur J Biochem 1997;247:625-634
39. Tréluyer J-M, Rey E, Sonnier M, Pons G, Cresteil T. Evidence of impaired cisapride metabolism in neonates. Br J Clin Pharmacol 2001;52:419-425

CrossRefs are available in the online published version of this paper:
http://www.librapharm.com
Paper PPDT-0156_3, *Accepted for publication:* 17 May 2006
Published Online: 7 July 2006
doi:10.1185/146300906X105131