The Prokinetic Cinitapride Has No Clinically Relevant Pharmacokinetic Interaction and Effect on QT during Coadministration with Ketoconazole

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ABSTRACT:

The present clinical trial was designed to evaluate the possible pharmacokinetic and electrocardiographic interactions of the gastrointestinal prokinetic drug cinitapride with ketoconazole. The safety and tolerability of the study treatments were also evaluated. After a placebo-controlled, double-blind, crossover design, 16 healthy male (n = 8) and female (n = 8) volunteers were randomized into four treatment groups of four subjects (two males and two females): cinitapride (CTP; 1 mg t.i.d.) + ketoconazole (KET; 200 mg b.i.d.), CTP + placebo (PL), PL + KET, and PL + PL. Treatments were given for 7 days with a washout period of 14 days between crossover treatments. Cinitapride is rapidly absorbed after oral administration and is metabolized by the cytochrome P450 CYP3A4 and CYP2C8 isozymes. At steady state, coadministration with ketoconazole, a potent CYP3A4 inhibitor, increased mean Cmax,ss and AUC, by 1.63- and 1.98-fold, respectively. Measurement of mean QTc interval or baseline-corrected QTc intervals on day 7 showed small increases that were due to the effects of ketoconazole alone. Comparing CTP+KET versus PL+KET, the differences between mean increases in the QTc parameters were always less than 2 ms. Finally, no outlier increase of the QTc interval versus baseline >60 ms was identified after any treatment. The study showed that cinitapride, either given alone or after coadministration with ketoconazole 200 mg b.i.d., had no effect on cardiac repolarization as measured by changes in the heart rate-corrected QT interval on the surface electrocardiogram.

Cinitapride is a substituted benzamide gastrointestinal prokinetic agent acting via complex, but synergic effects on serotonergic 5-HT2 (inhibition) and 5-HT4 (stimulation) receptor and dopaminergic D2 (inhibition) receptors in the neuronal synapses of the myenteric plexus (Roberts, 1982; Fernandez and Massingham, 1985; Massingham et al., 1985). The pharmacology, pharmacokinetics, toxicology, and clinical profile of cinitapride have been reviewed (Fernandez and Roberts, 1991). Cinitapride has been marketed in Spain under the trade names Cidine and Blaston since November 1990, and is available in Mexico under the name Pemix. The current indications include gastroesophageal reflux and functional disorders in gastrointestinal motility (de-}

ABBRévIATIONS: MS/MS, tandem mass spectrometry; QT, duration in milliseconds from the beginning of Q wave to the end of the T wave; CTP, cinitapride; KET, ketoconazole; PL, placebo; AUC, area under the plasma concentration-time curve within a dosing interval; QTc, QT interval corrected for heart rate; ECG, electrocardiogram; FI, fluctuation index; RR, duration in milliseconds between two R peaks of two consecutive QRS complexes; PR, duration in milliseconds from the beginning of wave P to onset of ventricular depolarization (Q and R); QRS, duration in milliseconds of the QRS complex; QT interval corrected by the Bazett formula (QT/RR1/2); QTcF, QT interval corrected by the Fridericia formula (QT/RR120); QTcl, QT linear correction model [QT + α × (1 – RR)]; QTcI, QT parabolic log/log correction model (QT/RR*); hERG, human ether-a-go-go-related gene; ANOVA, analysis of variance; CI, confidence interval; AE, adverse event.
try (MS/MS) with a limit of quantification of 0.1 ng/ml that allowed an appropriate characterization of the pharmacokinetic profile of cinitapride under conditions known to favor arhythmogenesis with cisapride. Such conditions are those where the metabolism of cisapride is inhibited, especially by coadministration with drugs blocking the cytochrome P450 CYP3A4 isozyme, such as macrolide antibiotics and antifungal azoles (Michalets and Williams, 2000; Jones et al., 2001). Under these circumstances, the metabolism of cisapride is prevented and the drug accumulates in plasma leading to concentrations sufficient to block the rapid component of the delayed rectifier potassium current passing through the cardiac hERG channel (Rampe et al., 1997). This results in a prolongation of the repolarization phase of the cardiac action potential (measured as a prolongation of the heart rate-corrected QTc interval of the surface electrocardiogram), which in turn is thought to facilitate reentry phenomenon and early after depolarization (Puisieux et al., 1996) favoring the induction of torsade de pointes arrhythmias.

In fact, according to a recent review of the relationships between preclinical electrophysiology, clinical QT interval prolongation, and torsade de pointes for some 52 diverse drugs (Redfern et al., 2003), it was considered prudent to investigate the electrocardiographic effects of cinitapride under conditions known to favor arrhythmogenesis with cisapride. Another important objective was to evaluate the safety and tolerability of the study treatments, particularly the effects on the QT interval.

Materials and Methods

Ethics. Written notification of approval was obtained from the Independent Ethics Committee and given to the investigator before starting the study, which was performed according to the regulations of the German Medicines Act, the directives of the Declaration of Helsinki for biomedical research in humans, revised version of Edinburgh (Scotland, October 2000), and the announce-ments for the Principles for Correct Implementation of Clinical Trials of the International Conference on Harmonisation-Good Clinical Practice Guide-

Before enrollment, all subjects were comprehensively informed about the trial (procedures, pharmacological effects, adverse events, consequences, risks, and hazards) and about their right to withdraw at any time without specifying reasons. All subjects gave their written informed consent before participation.

Study Design. The study was a phase I, single center, randomized, placebo-controlled, double-blind, double-dummy, multiple-dose, crossover clinical trial with four treatments, periods, and sequences. William’s design (Jones and Kenward, 1989) was used for the assignment of treatment sequences.

Subjects. Sixteen healthy male (n = 8) and female (n = 8) subjects, complying with the inclusion criteria (age 18–50 years; body mass index between 17 and 29.9 kg/m²) completed the study. At screening, subjects did not present any clinically significant abnormalities in physical examinations, vital signs, body temperature, ECGs (QTc Bazett <440 ms), and laboratory tests. Anthropometric data on subjects at screening are detailed in Table 1. The proportions of smokers, regular alcohol drinkers, and stimulant users were 59%, 65% and 34%, respectively.

Treatment Plan. Eligible subjects (16) were randomized into four groups of two males and two females to receive multiple doses of either cinitapride (CTP) + ketoconazole (KET), CTP + placebo (PL), PL + KET, or PL + PL for 7 days with a washout period of 14 days between treatments. All medications and placebo were produced by Laboratorios Almirall, S.A. The doses of cinitapride (1 mg t.i.d.) and ketoconazole (200 mg b.i.d.) were chosen based on the fact that 1 mg three times daily is the recommended therapeutic dose for cinitapride, and although 400 mg q.d. or 200 mg b.i.d. are the recommended maximum daily doses for ketoconazole, the higher single dose posology is not used clinically and has been shown to have, itself, a significant effect on the QTc interval (Chaikin et al., 2005) that would confound the object of the study.

In any event, the dose of 200 mg even once daily has been used for interaction studies with many other drugs including the classic study with terfenadine in which the maximum plasma concentrations of unchanged drug increased from undetectable (<5 ng/ml) to 25 to 55 ng/ml in four subjects and in one subject...
from 7 ng/ml to 81 ng/ml (Honig et al., 1993), indicating a high level of enzyme inhibition. The posology of 200 mg q.d. is still being used, as are those of 200 mg b.i.d. and 400 mg q.d., and both of these latter regimens may be expected to reach similar steady-state levels of enzyme inhibition. On day 1, a single oral dose of cinitapride was given to the volunteers to get information on the pharmacokinetics of a single oral dose never observed before, since the liquid chromatography methods used in the past to measure cinitapride could not detect the cinitapride in plasma compared with the liquid chromatography and tandem mass spectrometry method used in this study. Cinitapride was given as an oral solution, whereas ketoconazole and its placebo were administered as tablets. Five milliliters of cinitapride oral solution (0.2 mg/ml) followed by 50 ml of water were administered daily for 7 days at 8:00 AM (before breakfast), 4:00 PM, and 12.00 AM. On day 1, only the morning dose of cinitapride was administered. Ketoconazole tablets (or matching placebo tablets) were administered for 7 days at 10:15 AM (immediately after breakfast) and at 10:15 PM (immediately after supper); tablets were taken with 100 ml of water. Meals were served at 10:00 AM (breakfast), 2:00 PM (lunch), 6:00 PM (snack), and 10:00 PM (supper). The same schedule of meals was kept from day 2 to day 8, and in each study period, the daily meals were identical. Meals administered on study days 1 and 7 were identical. The duration of 7 days for coadministration of cinitapride and ketoconazole was considered to be appropriate to attain sufficient enzyme inhibition, as well as steady-state pharmacokinetics for both drugs, and the 14-day washout was considered to be sufficient to ensure complete elimination of drugs and metabolites. No concomitant therapy was allowed during the study, except for treatment of adverse events.

**Pharmacokinetics.** Plasma samples. On days 1 and 7 of each study period, blood samples of 5 ml each were drawn by venous puncture or indwelling venous catheter and transferred into Li-heparinized Monovettes (Sarstedt AG & Co., Nümbrecht, Germany) at the following times: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 23.5 h postdose. On days 2 to 6, a blood sample was taken before the first morning cinitapride dose. Blood samples were centrifuged at 3000g and 4°C for 10 min within 15 min of collection, and the plasma was separated and frozen at −20°C until analysis.

**Drug assay.** Plasma concentrations of cinitapride were determined by TNO BIBRA International Ltd. (Carshalton, Surrey, UK) using liquid chromatography–MS/MS. Plasma (0.5 ml) was aliquoted into 1.5-ml Eppendorf tubes and 25 µl (0.2 µg/ml) of the internal standard (clebopride; CAS registry number 55905-53-8) were added to each tube, mixed, and centrifuged. The content of each sample was then transferred to a vial and injected onto a BioTrap 500 MS column (ChromTech Ltd., Congleton, Cheshire, UK) using 4% (v/v) 2-propanol in water. The column was then transferred to a vial and injected onto a BioTrap 500 MS column (Waters, Milford, MA) equipped with a BioTrap 500 MS column (Waters, Milford, MA) equipped with a BioTrap 500 MS column (Thermo Fisher Scientific, Runcorn, Cheshire, UK) using a mobile phase of acetonitrile/water/0.25% ammonia (55:45:5 v/v/v) at 1 ml/min. Under these conditions, the internal standard eluted at 3.0 to 3.2 min and cinitapride at 4.0 min.

**Determination of pharmacokinetic parameters.** Individual plasma concentration–time data were used to calculate the pharmacokinetic parameters using a model-independent approach. The maximum concentration (Cmax) and time to Cmax (Tmax) were taken from the observed values. The terminal elimination constant (λz) was estimated by linear least-squares regression analysis of the log-linear plot of plasma concentration–time data. The elimination half-life was obtained as t1/2 = ln(2)/λz versus time for the terminal calculated using the linear trapezoidal method, and the elimination half-life (t1/2) was calculated from the elimination rate constant. AUC from 0 to 8 h postdosing (AUC0–8) was calculated using the linear trapezoidal rule. AUC to infinity (AUC) was only determined for day 1 using the elimination rate constant. On study day 7 the following parameters were also calculated: trough plasma concentration (Cmin,ss), average plasma concentration (Cav,ss = AUC/t), maximum plasma concentration (Cmax,ss), time to maximum steady-state concentration (tmax,ss), area under the concentration-time curve (AUC), terminal elimination half-life (t1/2), fluctuation index (FI = (Cmax − Cmin)/Cav,ss) · 100, and accumulation ratio (AUC/AV,ss). All pharmacokinetic parameters have been tabulated together with their descriptive statistics: mean, standard deviation (S.D.), number of samples, and maximum and minimum values. The dosing interval τ in this particular study was 8 h and, therefore, AUCτ,∞ is equal to AUC∞.

### Statistical Analysis

Safety. The safety was evaluated by adverse events, physical examination, vital signs, clinical laboratory tests, 12-lead ECG, and continuous cardiac telemetry.

The 12-lead ECGs were recorded at screening and on day 8 of each study period before the subjects left the research unit. Continuous cardiac telemetry was performed on all subjects in all study periods, which started predose on day 1 until day 8, i.e., approximately 24 h after the last dosing.

For safety assessments, ECG readings were performed automatically (as recorded in the ECG printout). The following parameters were recorded by automatic device: heart rate (beats per minute), RR, PR, QRS, QT, and QTcB (QTcB = QT/√RR, Bazett formula) in milliseconds. Only clinically significant findings were to be recorded as an adverse event.

### Pharmacokinetics analyses.**

The comparison of AUCτ,∞, AUC, and Cmax between treatment groups (CYP3A4 and CYP2C19), assuming a 30% CV of AUC values, and a correlation coefficient between treatment periods of 0.7, with a 0.05 two-sided significance level.

**Pharmacokinetics analyses.** The relationship between QT and RR was evaluated by adverse events, physical examination, vital signs, clinical laboratory tests, 12-lead ECG, and continuous cardiac telemetry.

For each treatment, Pearson and Spearman rank correlation coefficients between QT and RR were also estimated by sex and overall.

Manual QT intervals were corrected by means of the following four different models (Bazett, 1920; Fridericia, 1920; Malik and Camm, 2001; Batchvarov et al., 2002; Malik et al., 2002; ICH Guidance for Industry E14, 2005).

- **Model A:** Linear QTcL = QT + α × (1 − RR)
- **Model B:** Individualized parabolic log/log QTcL = QT/RR
- **Model C:** Fixed parabolic log/log model (α = 1/2) (Bazett) QT = β × RR
- **Model D:** Fixed parabolic log/log model (α = 1/3) (Fridericia) QT = β × RR

For each subject and QT correction model, the relationship between QT and RR intervals was described by means of the corresponding regression models: 1. **Model A:** Linear model QT = β + α × RR 2. **Model B:** Individualized parabolic log/log model QT = β × RR
3. Model C: Fixed parabolic log/log model ($\alpha = 1/2$) (Bazett) $QT = \beta \times RR^{1/2}$
4. Model D: Fixed parabolic log/log model ($\alpha = 1/3$) (Fridericia) $QT = \beta \times RR^{1/3}$

In each case, the QT and RR interval values for each subject were derived from the ECGs corresponding to the drug-free periods. The $\alpha$ parameter of heart rate correction in models A and B was calculated for each subject under conditions where the correlation coefficient between QTc values and RR values equaled 0 (i.e., when the QTc interval was completely independent of heart rate). The $\alpha$ parameter of heart rate correction in models A and B and $\beta$ coefficient for each subject were calculated by means of the SAS nonlinear procedure (PROC NLIN; SAS Institute, Cary, NC).

The appropriateness of individual $\alpha$ values was studied for each subject by means of the Pearson and Spearman rank correlation coefficient ($\rho$) analysis between the values of RR and QT corrected according to the models described above. If $\rho$ was not significantly different from zero ($\rho > 0.05$), then the corresponding $\alpha$ value was considered appropriate for that particular subject.

For each QT correction model, QTc mean values and mean changes from baseline in QTc were compared between treatments by means of the Wilcoxon signed rank test overall and by sex.

Differences between treatments in QTc mean, mean changes from baseline QTc mean, and mean normalized areas were also analyzed by means of an ANOVA model for factorial designs. Treatment and interaction effects in this factorial model were estimated by least square means with S.E.M. and 95% confidence interval (95% CI). In all statistical tests, the probability of type I error was set at 0.05 two-tailed.

Results

Of the 17 subjects initially enrolled in the study, 16 completed all four treatment periods. One subject withdrew from the study at his own request. All subjects fulfilled the inclusion criteria and none of them met an exclusion criterion. Subjects were between 18 and 49 years old, their body weight was 44.6 to 101.8 kg, their height 1.56 to 1.94 m, and body mass index 18.1 to 29.5 kg/m² (Table 1).

Safety. No changes were observed in physical examination parameters during the trial compared with screening. Forty-two ($n = 42$) treatment-emergent adverse events (AEs) corresponding to 44 AE episodes occurred in 15 (88.2%) of the 17 study participants. There were no severe AEs or withdrawals due to these events. The percentage of subjects with any AE was 35.3% for CTP+PL, 50% for CTP+KET, 50% for KET+PL, and 43.8% for PL+KET. No differences were observed between male and female volunteers with regard to the number of subjects presenting any AE (8 of 17 and 7 of 17, respectively) or total number of AEs (21 AEs with 22 episodes in both sexes). All AEs were of mild or moderate intensity. Except for one AE (headache of moderate intensity) medically treated with a single 500-mg dose of paracetamol, all AEs had resolved spontaneously by 24 h after the last dose). Continuous cardiac telemetry did not reveal clinically significant findings in the judgment of the investigator.

Pharmacokinetics. Plasma concentration-time profiles of cinitaipride after the administration of a single oral dose of 1 mg on days 1 (a) and 7 (b) of treatment with and without ketoconazole are presented in Fig. 1. On day 1 of treatment, concentrations of cinitaipride were highly variable with mean ($\pm$S.D.) $C_{\text{max}}$ values of 0.33 $\pm$ 0.17 ng/ml (CTP+PL) and 0.41 $\pm$ 0.25 ng/ml (CTP+KET) and mean ($\pm$S.D.) AUC$_{0-8}$ of 1.05 $\pm$ 1.24 ng·h/ml (CTP+PL) and 1.43 $\pm$ 1.94 ng·h/ml (CTP+KET). No differences related to the coadministration of ketoconazole were detected in the cinitaipride absorption rate, with the mean ($\pm$S.D.) $t_{\text{max}}$ values being 1.4 $\pm$ 0.6 h (CTP+PL) and 1.5 $\pm$ 0.6 h (CTP+KET). No reliable estimates for the elimination kinetics could be obtained in any volunteer because of the low plasma concentrations during this phase. Steady-state pharmacokinetics was achieved by day 3 with cinitaipride alone and cinitaipride with ketoconazole (Fig. 2). On day 7 of treatment, concentrations of cinitaipride were detected in all subjects, being less variable and higher than those on day 1. The mean ($\pm$S.D.) $C_{\text{max,ss}}$ was 0.20 $\pm$ 0.12 ng/ml (CTP+PL) and 0.40 $\pm$ 0.22 ng/ml (CTP+KET), and mean ($\pm$S.D.) AUC$_{ss}$ was 3.05 $\pm$ 1.77 ng·h/ml (CTP+PL) and 5.33 $\pm$ 2.91 ng·h/ml (CTP+KET). The accumulation factors were 2.9 (CTP+PL) and
3.7 (CTP+KET) (Table 2). Other parameters such as $t_{\text{max}}$ remained unchanged at steady state compared with day 1 of treatment. Ketoconazole moderately increased cinitapride AUC$_{r,ss}$ and $C_{\text{max,ss}}$ by 1.98- and 1.63-fold, respectively (see Table 3).

The increase in CTP concentrations after coadministration with KET was statistically significant for $C_{\text{max,ss}} (p < 0.001)$ and AUC$_{r,ss}$ ($p < 0.001$) (Table 3). CTP concentrations were slightly higher in women, although relative increases due to KET inhibition were similar in males and females (data not shown).

**Pharmacodynamics.** The pharmacodynamic evaluation in this study comprised a thorough evaluation of the QTc after multiple-dose treatment with cinitapride alone or in combination with ketoconazole.

No relevant findings were observed in the standard ECG parameters. Minor rhythm and/or conductance disturbances were observed as isolated episodes. The morphology of the ECGs was considered as being normal and there were no signs of clinically significant abnormalities in any of the ECG traces.

A statistically significant correlation was found between QT and RR in all treatment groups, and that pattern was not modified by being normal and there were no signs of clinically significant abnormalities. The morphology of the ECGs was considered as being normal and there were no signs of clinically significant abnormalities in any of the ECG traces.

**It is for this reason that the double delta QT (this is mean changes from baseline QTc mean) is the recommended variable to be considered for calculating effects on the QT (ICH Guidance for Industry E14, 2005).**

When comparing the QTc means, or the mean changes from baseline QTc mean on day 7 of treatment, a small increase in QTc was observed (Tables 4 and 6). Treatment comparisons including cinitapride treatment indicated much smaller variations in QTc that were within approximately −0.8 to 1.7 ms for all QTc parameters used for the comparison of the treatment CTP+PL versus PL+PL (Table 4). Moreover, the mean increases in these QTc parameters were always below 2 ms, if the treatments CTP+KET versus KET were compared.

These differences are clinically irrelevant and mainly due to QTc variability and small sample size. Further analysis by means of factorial ANOVA models showed that these increases were due to the effect of ketoconazole alone (statistically significant in models A, B, and D, overall and in women). No significant effect was observed for any interaction cinitapride-ketoconazole in any of the factorial models fitted. Thus, the factorial model analysis results suggest that cinitapride does not induce QTc prolongation either when given alone or during coadministration with ketoconazole 200 mg b.i.d.

No outlier >60 ms was identified after any treatment (data not shown) and no subject had a QTc >500 ms (see ICH Guidance for Industry E14, 2005). Thus, in this trial, cinitapride has not shown any potential for inducing QT changes at therapeutic doses of 1 mg t.i.d.

Heart rate showed similar mean values for all four treatment regimens. No correlation was found between QTc and RR in each QT correction model with correlation coefficients ($r^2$) ranging from 0.02 to 0.04 using Pearson’s analysis and 0.03 to 0.07 using Spearman’s analysis. No trends toward sex differences were observed. Finally, no correlation was found between QTc or delta QTc and cinitapride.
plasma levels (matched data) in the four QT correction models (data not shown).

**Discussion**

Drug interactions with inhibitors of the cytochrome P450 system have been shown to be of particular clinical importance for gastrokinetic agents such as cisapride (Destas et al., 2000) and H1-receptor antagonists such as astemizole and terfenadine (Dresser et al., 2000). Ketoconazole increases the plasma concentrations of drugs metabolized by CYP3A4, and this enzyme is known to be involved in the metabolism of cinitapride. By contrast to cisapride metabolism, CYP2C8 has been shown to also be an important enzyme in cinitapride metabolism and, although also inhibited by ketoconazole, in this case, the inhibition is weak compared with the inhibition of CYP3A4. Thus, the present study was designed to assess the influence of ketoconazole 200 mg b.i.d on the pharmacokinetics and cardiac safety of therapeutic doses of cinitapride 1 mg t.i.d. The presence of ketoconazole resulted in only a small increase in cinitapride plasma concentrations as reflected by a 1.63-fold increase in steady-state Cmax and a 1.98-fold increase in AUC0-∞ without prolongation of the t1/2max. This finding supports the conclusion that CYP2C8 retains some capacity for removing cinitapride from blood despite the effect of ketoconazole blocking CYP3A4-mediated metabolism. A study carried out in the urine obtained in the present study demonstrated that oxidative metabolism occurs and that conjugation was also an important pathway contributing to the rapid clearance of the molecule (De Graeve, 2001).

As a consequence, the safety profile of cinitapride also appears to be unaffected by concomitant administration of ketoconazole as suggested by the similar incidence and intensity of AEs in both treatment groups. Forty-two (n = 42) treatment-emergent AEs corresponding to 44 AE episodes occurred in 15 (88.2%) of 17 subjects of the safety evaluation. There were no serious adverse events or withdrawals due to AEs. No treatment-related effects were observed for mean QTc

**TABLE 4**

**Comparisons of QTc means and mean changes from baseline QTc mean between treatments (mean ± S.E.M.)**

Models are: A, linear, QTcL; B, parabolic log/log, QTcI; C, fixed parabolic log/log (α = 0.5), QTcB (Bazett); D, fixed parabolic log/log (α = 0.33), QTcF (Fridercia).

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
<th>Model D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP+KET vs. CTP+PL</td>
<td>5.11 ± 1.85 (0.0135)</td>
<td>5.17 ± 1.87 (0.0135)</td>
<td>3.56 ± 2.25 (0.2114)</td>
<td>4.78 ± 1.79 (0.0149)</td>
</tr>
<tr>
<td>CTP+KET vs. PL+KET</td>
<td>0.85 ± 2.78 (0.5282)</td>
<td>0.89 ± 2.84 (0.5282)</td>
<td>0.90 ± 3.03 (0.7719)</td>
<td>1.19 ± 2.81 (0.5282)</td>
</tr>
<tr>
<td>CTP+PL vs. PL+PL</td>
<td>4.66 ± 2.49 (0.1167)</td>
<td>4.80 ± 2.53 (0.1167)</td>
<td>2.75 ± 2.63 (0.4332)</td>
<td>4.38 ± 2.45 (0.1167)</td>
</tr>
<tr>
<td>CTP+PL vs. PL+KET</td>
<td>−4.27 ± 2.78 (0.1971)</td>
<td>−4.28 ± 2.80 (0.1971)</td>
<td>−2.66 ± 2.87 (0.2979)</td>
<td>−3.59 ± 2.75 (0.2522)</td>
</tr>
<tr>
<td>PL+KET vs. PL+PL</td>
<td>−0.45 ± 2.56 (0.9399)</td>
<td>−0.38 ± 2.62 (0.8999)</td>
<td>−0.81 ± 2.72 (0.5619)</td>
<td>−0.40 ± 2.65 (0.8603)</td>
</tr>
<tr>
<td>PL+KET vs. PL+PL</td>
<td>3.81 ± 1.72 (0.0577)</td>
<td>3.90 ± 1.79 (0.0634)</td>
<td>1.85 ± 1.44 (0.2512)</td>
<td>3.19 ± 1.73 (0.0833)</td>
</tr>
</tbody>
</table>

**TABLE 5**

**Mean changes from baseline QTc mean (ms)**

Models are: A, linear, QTcL; B, individualized parabolic log/log, QTcI; C, fixed parabolic log/log (α = 0.5), QTcB; D, fixed parabolic log/log (α = 0.33), QTcF.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP+KET All</td>
<td>−8.2 ± 2.8</td>
<td>−8.2 ± 2.9</td>
<td>−3.4 ± 2.8</td>
<td>−7.2 ± 2.8</td>
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<tr>
<td>Males</td>
<td>−6.0 ± 5.3</td>
<td>−5.9 ± 5.3</td>
<td>−0.4 ± 5.1</td>
<td>−4.3 ± 5.1</td>
</tr>
<tr>
<td>Females</td>
<td>−10.3 ± 2.3</td>
<td>−10.4 ± 2.4</td>
<td>−6.4 ± 2.4</td>
<td>−10.1 ± 2.3</td>
</tr>
<tr>
<td>CTP+KET All</td>
<td>−2.1 ± 2.8</td>
<td>−2.2 ± 2.8</td>
<td>0.7 ± 3.0</td>
<td>−1.5 ± 2.8</td>
</tr>
<tr>
<td>Males</td>
<td>−1.2 ± 4.9</td>
<td>−1.4 ± 4.8</td>
<td>1.9 ± 4.5</td>
<td>−0.4 ± 4.9</td>
</tr>
<tr>
<td>Females</td>
<td>−3.0 ± 3.0</td>
<td>−3.0 ± 3.2</td>
<td>−0.5 ± 4.3</td>
<td>−2.7 ± 2.9</td>
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<tr>
<td>PL+KET All</td>
<td>−2.5 ± 2.2</td>
<td>−2.5 ± 2.3</td>
<td>−1.1 ± 2.5</td>
<td>−2.4 ± 2.2</td>
</tr>
<tr>
<td>Male</td>
<td>−2.5 ± 2.3</td>
<td>−2.5 ± 2.4</td>
<td>−2.2 ± 2.6</td>
<td>−3.3 ± 1.7</td>
</tr>
<tr>
<td>Females</td>
<td>−2.6 ± 4.0</td>
<td>−2.6 ± 4.1</td>
<td>−0.0 ± 4.5</td>
<td>−1.5 ± 4.1</td>
</tr>
<tr>
<td>PL+PL All</td>
<td>−9.6 ± 2.5</td>
<td>−9.7 ± 2.5</td>
<td>−3.8 ± 2.8</td>
<td>−8.8 ± 3.0</td>
</tr>
<tr>
<td>Males</td>
<td>−12.3 ± 4.2</td>
<td>−12.4 ± 4.2</td>
<td>−3.7 ± 4.9</td>
<td>−10.6 ± 5.6</td>
</tr>
<tr>
<td>Females</td>
<td>−6.9 ± 2.6</td>
<td>−6.9 ± 2.7</td>
<td>−3.8 ± 2.9</td>
<td>−7.1 ± 2.7</td>
</tr>
</tbody>
</table>
changes on day 7 compared with screening. Continuous cardiac telemetry did not reveal clinically significant findings in the judgment of the investigator.

Detailed evaluation of the possible potential of cinitapride to induce a QTc prolongation involved the use of four different QT correction models applied to the manually evaluated ECGs before and on day 7 of the four study treatments. There is an ongoing discussion about the most appropriate method(s) for correcting QT interval for changes in heart rate. In this article, we have employed the two most used population methods of QT correction [Bazett and Fridericia, models C and D (Bazett, 1920; Fridericia, 1920)] and two models of subject-specific QT correction [linear and individualized log/log, models A and B (Malik and Camm, 2001; Malik et al., 2002)].

Mean QTc changes from mean baseline values showed a decrease for all treatments with all four correction models (except for QTcB when given with placebo or when given with ketoconazole 200 mg b.i.d. This is in contrast with previous findings with cisapride, a gastroprokinetic drug that has been associated with pronounced QTc prolongation and fatal arrhythmias.

### References


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