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Co-administration of ketoconazole with H_1-antagonists ebastine and loratadine in healthy subjects: pharmacokinetic and pharmacodynamic effects

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Aims
Two studies were conducted to evaluate the effects of coadministration of ketoconazole with two nonsedating antihistamines, ebastine and loratadine, on the QTc interval and on the pharmacokinetics of the antihistamines.

Methods
In both studies healthy male subjects (55 in one study and 62 in the other) were assigned to receive 5 days of antihistamine (ebastine 20 mg qd in one study, and loratadine 10 mg qd in the other) or placebo alone using a predetermined randomization schedule, followed by 8 days of concomitant ketoconazole 450 mg qd/antihistamine or ketoconazole 400 mg qd/placebo. Serial ECGs and blood sampling for drug analysis were performed at baseline and on study days 5 (at the end of monotherapy) and 13 (at the end of combination therapy). QT intervals were corrected for heart rate using the formula $QTc = QT/RR^{\alpha}$ with special emphasis on individualized α values derived from each subject's own QT/RR relationship at baseline.

Results
No significant changes in QTc interval from baseline were observed after 5 days administration of ebastine, loratadine or placebo. Ketoconazole/placebo increased the mean QTc (95% CI) by 6.96 (3.31–10.62) ms in the ebastine study and by 7.52 (4.15–10.89) ms in the loratadine study. Mean QTc was statistically significantly increased during both ebastine/ketoconazole administration (12.21 ms; 7.39–17.03 ms) and loratadine/ketoconazole administration (10.68 ms; 6.15–15.21 ms) but these changes were not statistically significantly different from the increases seen with placebo/ketoconazole (6.96 ms; 3.31–10.62 ms), $P = 0.08$ ebastine study, (7.52 ms; 4.15–10.89 ms), $P = 0.26$ loratadine study). After the addition of ketoconazole, the mean area under the plasma concentration–time curve (AUC) for ebastine increased by 42.5 fold, and that of its metabolite carebastine by 1.4 fold. The mean AUC for loratadine increased by 4.5 fold and that of its metabolite desloratadine by 1.9 fold following administration of ketoconazole. No subjects were withdrawn because of ECG changes or drug-related adverse events.

Conclusions
Ketoconazole altered the pharmacokinetic profiles of both ebastine and loratadine although the effect was greater for the former drug. The coadministration of ebastine with ketoconazole resulted in a non significant mean increase of 5.25 ms (–0.65 to

11.15 ms) over ketoconazole with placebo (6.96 ms) while ketoconazole plus loratadine resulted in a nonsignificant mean increase of 3.16 ms (–2.73 to 8.68 ms) over ketoconazole plus placebo (7.52 ms). Changes in uncorrected QT intervals for both antihistamines were not statistically different from those observed with ketoconazole alone. The greater effect of ketoconazole on the pharmacokinetics of ebastine was not accompanied by a correspondingly greater pharmacodynamic effect on cardiac repolarization.

Introduction

The last decade has seen the removal of some eight noncardiovascular drugs from the market because of their association with the occurrence of the potentially fatal polymorphic tachycardia known as torsade de pointes [1].

The extreme rarity of this arrhythmia, together with the evidence that it is related to, although not necessarily caused by, a prolongation of the QT interval on the surface electrocardiogram [2], has resulted in the extensive use of this parameter as a surrogate marker for torsade de pointes.

In the case of the antihistamine, terfenadine, the phenomenon was identified after many years of uneventful use, as occurring after overdosage or metabolic inhibition resulting from hepatic insufficiency or coadministration with drugs inhibiting CYP3A4 activity [3]. Under normal circumstances this enzyme system rapidly converts terfenadine to its active acid metabolite, fexofenadine, which is apparently devoid of the arrhythmogenic properties of the parent drug [4].

Ketoconazole is a commonly prescribed antifungal agent and a potent inhibitor of CYP3A4. When coadministered with terfenadine it produces large increases in plasma drug C_{max} concentrations (from virtually undetectable to 25–80 ng ml^{-1}). This is accompanied by equally significant increases in the prolongation effects on the corrected QT intervals (QTc), from an innocuous trough mean of 8 ms to a potentially arrhythmogenic trough mean of 82 ms, together with serious changes in the morphology of the T wave [5].

Ebastine is a more recent nonsedating antihistamine which, in contrast to terfenadine, has no effect on the QTc interval at normal therapeutic doses of 10 or 20 mg once daily (qd). At high doses (100 mg qd), ebastine causes a small increase in heart rate which leads to a shortening of the QT interval, but also to an overcorrection when the usual but imprecise Bazett square root formula [6] is used [7]. The resulting small increase in the QTc interval is not seen when the less common Fridericia cube root formula [8] is used, nor when the more logical specific population or individualized formulae are used [7, 9, 10].

Ebastine, like terfenadine, undergoes significant first pass metabolism via CYP3A4 to an active metabolite, carebastine, and this pathway is inhibited by ketoconazole [11].

Loratadine, another widely used antihistamine, appears not to be associated with the induction of torsade de pointes. It also undergoes metabolism via CYP3A4 and, to a lesser extent, CYP2D6, with the formation of the active metabolite, desloratadine [12]. The pharmacokinetics of loratadine is also affected by the coadministration of ketoconazole although not nearly as much as that of terfenadine, and with no electrocardiographic consequences [13].

The aim of the study was to compare the effects of ketoconazole on the pharmacokinetics and pharmacodynamics (QTc) of ebastine and loratadine administered at maximum recommended doses.

Materials and methods

Study design

Two separate studies, one with ebastine and one with loratadine, were conducted at different times and in different populations. The studies were of a blinded, parallel group, placebo-control design. The loratadine study was double-blinded, whereas for ebastine, the study treatments were dosed by a third party in order to blind the investigator and all other study personnel. The objective of the studies was to assess the electrocardiographic effects of therapeutic doses of ebastine (20 mg qd) and loratadine (10 mg qd), each against placebo, when given alone for 5 days and when administered with ketoconazole for an additional 8 days. Therefore, the dosing schedule in both studies was 13 days of treatment with antihistamine or placebo with ketoconazole being added from day 6 onwards. Other objectives were to evaluate changes in the pharmacokinetics of the antihistamines and their primary active metabolites when administered concomitantly with ketoconazole, and to characterize the relationships between plasma concentrations of ebastine and loratadine and their primary metabolites, carebastine and desloratadine and the potential for QTc prolongation. The study protocols were approved by an investigational review board (Inde-

pendent Investigational Review Board Inc, Florida USA, for the ebastine study, and Comité Consultatif de Protection des Personnes dans la Recherche Biomédical, Paris, France for the loratadine study) and all subjects provided written informed consent.

Study populations

Eligible subjects included healthy males between the ages of 18 and 40 years who were within ±15% of their ideal body weight (Metropolitan Life Tables), were non-smokers for at least the previous three months, and who did not have any specific ECG abnormalities on the 12-lead surface electrocardiogram.

Study procedures

In each of the two studies, subjects stayed in the research unit for baseline ECG evaluations from day −2 to day 1 (first day of drug administration). Standardized meals were provided at set intervals throughout the study. On day −1, baseline serial ECGs were performed at the same times as on day 5. On day 1, eligible subjects were assigned, following a predetermined randomization schedule provided by our statisticians, to receive drug or placebo, once daily after breakfast, and were then required to attend the research unit on days 2–4 to receive their test medication. Subjects spent days 4–14 in the research unit. On day 5, serial ECGs and blood sampling for drug analysis were performed at 0, 1, 2, 4, 6, 8, 12, and 24 h after dosing for the ebastine study, and at 0, 1.5, 2, 3, 5, 8, 12, and 24 h after dosing for the loratadine study. From day 6 to day 13, all subjects received a single 400 mg daily dose of ketoconazole (Nizoral®, Janssen, Titusville, NJ, USA) in addition to ebastine, loratadine or placebo. This dose of ketoconazole, although unusual in clinical practice, is the maximum permitted dose according to the label and was used at the insistence of the US Food and Drug Administration (FDA). During the 8 days of ketoconazole administration, cardiac monitoring was performed using continuous telemetry and periodic ECG measurements (predose, 2, 5 or 6 and 12 h postdose). Predose blood samples were also drawn to determine trough antihistamine concentrations. After the final dose of ketoconazole on day 13, patients underwent 24 h measurement of serial ECGs and blood sampling for drug analysis as described for day 5. Follow-up ECGs and blood sampling were planned to be performed on an outpatient basis for any subject with a mean QTcB more than 10% greater than their mean baseline QTcB on day −1.

Subjects were instructed to report any adverse events directly to study personnel or record them on a diary card. Vital signs (systolic/diastolic blood pressure, pulse rate) were assessed at screening, at day −2, at study discharge, and 5 or 6 h postdose on days 5, 8 or 9, 11, and 13.

ECG parameters

Electrocardiogram evaluations consisted of the following: 12-lead ECG (Leads I, II, III, aVR, aVL, aVF, V_1 to V_6); 10 second rhythm strip (Lead II); recording of heart rate, PR, QRS, QT, QTc and QRS axis. ECGs were analysed at a single site (Premier Research Worldwide, Philadelphia, PA) using a digitizer (Sigmascan, Jandel Scientific, Seattle, WA).

In each study all ECGs were read by the same cardiologist in blinded fashion. The Sigmascan system was calibrated for accuracy prior to each session by measuring a series of 1 mV, 40 ms blocks from the background ECG paper grid (25 mm s^{-1} paper speed). After calibration, the ECG to be measured was mounted and anchored to a Jandel Scientific Sigmascan digitizing pad to avoid movement. Using a jeweller's magnifying lamp, analysts used crosshair devices to measure the RR, PR, QRS and QT intervals. Interval measurements were performed across three consecutive cardiac cycles from the optimum technical portion of the Lead II tracing. QT was corrected for heart rate (QTc) using the parabolic log/log formula $QTc = \frac{QT}{RR^{\alpha}}$ where $\alpha = 0.25$ for Kawataki [14], 0.31 for Yoshinaga [15], 0.32 for Simonson [16], 0.33 for Fridericia [8], 0.38 for Hodges [17], 0.398 for Boudolas [18], 0.5 for Bazett [6] and 0.603 for Mayeda [19], but using individualized α-values derived from individual off-drug QT/RR relationships for each subject as previously described [9, 10]. This avoids the problem of using formulae based on populations other than the one under study, and allows for the considerable interindividual variability in the QT/RR relationships [20], but low intraindividual variability over time [21].

Mean postdose outlier QTc values were analysed for each subject according to the CPMP criteria [22], such that increases <30 ms are unlikely to cause significant concern, increases of 30–60 ms are likely to represent a drug effect, and increases >60 ms and/or absolute values >500 ms are likely to raise clear concerns about the potential risk of inducing arrhythmias including torsade de pointes. To look for sporadic extreme values, these criteria were additionally applied to each individual electrocardiogram.

Drug analysis

Serial blood samples were collected from all subjects regardless of treatment assignment (i.e. ebastine, lorat-

adine or placebo). Ten millilitre samples were collected following the ECG recordings at the time points described above via individual venipuncture using sodium heparin (ebastine study) or sodium EDTA (loratadine study) as anticoagulant.

The blood samples were centrifuged at 4 °C for 10 min at 2100 g and the separated plasma transferred (at least 2 ml) into two separate labelled polypropylene tubes with screw caps and frozen, within 30 min from time of collection, in an upright position at −20 °C or lower.

One set of frozen samples was transferred directly to the external analytical laboratory (Advance Analytical Biosciences Inc or MDS Pharma Services) and the other set was transported to Rhône-Poulenc Rorer and stored for any necessary future analyses.

Ebastine and carebastine were isolated from plasma by solid phase extraction and analysed using validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) in a positive ion spray mode [23].

Thawed plasma samples (0.5 ml) with added internal standard (terfenadine) were loaded onto conditioned C_2 SPE columns (Varian) and eluted with 1 ml of 0.1% triethylamine in methanol. The eluates were dried under nitrogen and reconstituted in 0.3–0.4 ml of acetonitrile: water (90 : 10). The mobile phase was acetonitrile: 10 mM ammonium acetate (90 : 10), flow rate 200 µl min^{-1}. The HPLC system used was a model LC-IOAD (Shimadzu, Baintree, MA, USA), and the chromatographic column was a 2 mm × 20 mm cyanopropyl guard cartridge (Keystone, Bellefonte, PA, USA). The run time was approximately 1.6 min with approximate retention times for ebastine, carebastine and terfenadine of 0.58 min, 0.92 min and 0.97 min, respectively. The API III^{plus} mass spectrometer (PE Sciex, Thornhill, ON, Canada) was operated in the positive ion mode and data were collected using selected reaction monitoring (SRM). The lower limits of quantification of ebastine and carebastine were 0.05 ng ml^{-1} and 1.00 ng ml^{-1}, respectively, with accuracies (as percentage of the nominal concentration of controls) of 98.8–108% and 90–110%, respectively, and precisions (established by the coefficients of variation of the controls) of ≤8.42% and ≤7.17%, respectively.

Loratadine and desloratadine were isolated from plasma by liquid-liquid extraction followed by derivatization and analysed using a validated and proprietary LC/MS/MS method [24].

Thawed plasma samples (1.0 ml) with added internal standard (prazepam) were mixed with 0.1 ml of 1 N Na0H, vigorously shaken with 8 ml of 5% hexane/isopropylether for 15 min and then centrifuged at 3025 g for 15 min at 10 °C. The upper organic layer was separated, dried at 40 °C under nitrogen, reconstituted with 0.3 ml of the derivatization solution, heated at 60 °C for 20 min, left to cool, dried at 40 °C under nitrogen and reconstituted with 0.4 ml methanol. The mobile phase was acetronitrile: 25 mM ammonium acetate: THF (68 : 30 : 2), delivered at a flow rate 1.0 ml min^{-1}. The HPLC system used was a model 1090 Series II (Hewlett Packard, Wilmington, DE, USA), and the chromatographic column was a 4.6 mm × 33 mm Supelcosil LC-18-DB column. The run time was approximately 2 min with approximate retention times for desloratadine, loratadine and prazepam of 0.57 min, 0.90 min and 1.01 min, respectively. The API III mass spectrometer (PE Sciex) was operated in positive ion mode, and data were collected using multiple reaction monitoring (MRM). The lower limit of quantification of both loratadine and desloratadine was approximately 0.1 ng ml^{-1}. The assays had accuracies of 93.5–102.2% and 92.9–104.3%, respectively, and precisions of <6.6% and <8.6%, respectively.

Pharmacokinetic analysis

Steady state parameters for each antihistamine and its metabolite were calculated using noncompartmental techniques. Twenty-four hour plasma concentration–time profiles (sampled after drug administration on days 5 and 13) were used to determine maximum and minimum plasma concentrations (C_{max}, C_{min}), and time to reach C_{max} (T_{max}). Steady state areas under the concentration–time curve (AUC) were calculated from the same data by linear trapezoidal summation. Half-lives ($t_{1/2}$) were calculated from the terminal elimination rate constants on days 5 and 13.

Statistical analysis

All subjects who completed the prescribed course of study medication were included in the primary analysis, which was performed using paired *t*-tests. The primary response variable was change in mean QTc from 0 to 12 h between day −1 (baseline) and days 5 and 13. *t*-tests were also used to compare individual treatments. In both studies a sample size of 60 (30 per treatment group) was originally chosen to provide a power of 90% to detect a mean change of about 15 ms from baseline QTcB between the antihistamine/ketoconazole groups and their respective placebo/ketoconazole groups, based on experience from previous studies where the standard deviation of QTcB values was 20 ml. The same statistical analyses were conducted for uncorrected QT and heart rate (HR). Pharmacokinetic parameters were analysed by ANOVA using the general linear models proce-

dure and linear regression analysis was used to investigate the pharmacokinetic/pharmacodynamic relationship. All pharmacokinetic tests were one-sided with a significance level of 0.05.

Results

The ebastine study comprised 55 subjects (mean age 31.7 years, range 21–24 years; mean weight ± SEM 77.5 kg ± 1.24 kg; height 175.0 ± 0.9 cm), and the loratadine study 62 subjects (mean age 25.0 years, range 18–38 years; mean weight ± SEM 74.86 ± 1.05 kg; height 178.0 ± 0.7 cm). There were no relevant differences in baseline characteristics between treatment groups. In the ebastine study, two subjects discontinued early for administrative reasons, and one for an adverse event not related to the study drug. In the loratadine study, two subjects withdrew their consent and discontinued early.

Tables 1 and 2 present the QTc interval data for each study. Neither ebastine, loratadine nor placebo had any significant effect on the QTc interval when administered alone for 5 days. However, following the administration of ketoconazole, an increase in QTc from baseline was observed in all (placebo and active) treatment groups.

In the ebastine study (Table 1), the coadministration of ketoconazole 400 mg qd with a 20 mg regimen of ebastine for 8 days resulted in a significant change in mean uncorrected QT (95% CI) of 6.59 ms (2.12–11.07) which was not significantly different ($P = 0.68$) from the significant change of 5.27 (0.58–9.96) ms with ketoconazole and placebo. Mean heart rate increased significantly by 3.41 bpm (1.49–5.33) after ebastine plus ketoconazole, a difference that was not significantly greater ($P = 0.076$) than the nonsignificant 1.03 bpm (–0.88 to 2.93) increase with placebo plus ketoconazole. The group mean (±SD) α-value was 0.32 (±0.146).

Co-administration of ketoconazole with ebastine resulted in a significant increase ($P < 0.00001$) in mean individualized QTc of 12.21 (7.39–17.03) ms. This increase was not significantly different ($P = 0.080$) from the significant increase of 6.96 (3.31–10.62) ms seen following coadministration of ketoconazole with placebo. The 95% confidence intervals of the 5.25 ms difference between the two treatments were –0.65 to 11.15 ms.

In the loratadine study (Table 2), coadministration with ketoconazole resulted in a mean 1.84 ms (–3.75 to 7.43) increase in uncorrected QT which was not statistically different ($P = 0.52$) from the value of 4.12 ms (–0.50 to 8.73) seen with ketoconazole with placebo. Mean heart rate increased significantly by 4.43 bpm (2.06–6.80) after coadministration, a value that was significantly different ($P = 0.043$) from the 1.37 (–0.49–3.23) bpm increase with placebo plus ketoconazole. The group mean (±SD) α-value was 0.28 (±0.133).

Co-administration of ketoconazole with loratadine resulted in a significant increase ($P < 0.00001$) in mean individualized QTc of 10.68 ms (6.15–15.21), a value

Table 1
Interaction between ketoconazole and ebastine: summary of mean change from baseline in QTc Interval

	Day	Treatment	Mean change from baseline	SEM	95% CI vs. placebo	P-Value*
Uncorrected	5	Placebo	–4.25	2.18	(–8.75, 0.25)	0.0629
QT (ms)	13	Placebo + Ketoconazole	5.27	2.28	(0.58, 9.96)	0.0292
	5	Ebastine	–4.47	2.33	(–9.27, 0.33)	0.0665
	13	Ebastine + Ketoconazole	6.59	2.17	(2.12, 11.07)	0.0056
Heart rate	5	Placebo	1.47	0.82	(–0.22, 3.15)	0.0862
(bpm)	13	Placebo + Ketoconazole	1.03	0.93	(–0.88, 2.93)	0.2760
	5	Ebastine	0.92	0.76	(–0.64, 2.48)	0.2360
	13	Ebastine + Ketoconazole	3.41	0.93	(1.49, 5.33)	0.0012
Individualized	5	Placebo	–1.90	1.51	(–5.00, 1.21)	0.2210
QTc (ms)	13	Placebo + Ketoconazole	6.96	1.78	(3.31, 10.62)	0.0006
	5	Ebastine	–2.20	2.11	(–6.55, 2.16)	0.3090
	13	Ebastine + Ketoconazole	12.21	2.34	(7.39, 17.03)	0.0000

* *Paired* t-*test. Two-sided test.* n = *26.*

that was not significantly different ($P = 0.26$) from the significant increase of 7.52 ms (4.15–10.89) seen following coadministration of ketoconazole with placebo. The 95% confidence intervals of the 3.16 ms difference between the two treatments were −2.73 to 8.68 ms.

None of the subjects in any of the studies had on an absolute QTc >500 ms. Considering increases in QTc from baseline 0/56, 0/26 and 0/30 subjects, and 0/392, 2/182 and 1/210 individual electrocardiograms showed increases greater than 60 ms following placebo/ketoconazole, ebastine/ketoconazole and loratadine/ketoconazole, respectively. Corresponding values for subjects and electrocardiograms with increases in QTc between 30 and 60 ms were 1/56, 4/26 and 2/30, and 17/392, 22/182 and 19/210, respectively.

Tables 3 and 4 present the pharmacokinetic data for ebastine and loratadine when administered alone for 5 days and concomitantly with ketoconazole for 8 days in separate studies.

Concentrations of loratadine and ebastine and their active metabolites were significantly increased when the drugs were administered with ketoconazole. Maximal ebastine concentrations were achieved between 1 and 4 h when the drug was given alone, and from 2 to

Table 2
Interaction between ketoconazole and loratadine: summary of mean change from baseline in QTc Interval

	Day	Treatment	Mean change from baseline	SEM	95% CI vs. placebo	P-Value*
Uncorrected	5	Placebo	–0.74	1.51	(–3.83, 2.35)	0.6290
QT (ms)	13	Placebo + Ketoconazole	4.12	2.26	(–0.50, 8.73)	0.0783
	5	Loratadine	–3.40	2.36	(–8.24, 1.43)	0.1600
	13	Loratadine + Ketoconazole	1.84	2.73	(–3.75, 7.43)	0.5060
Heart rate	5	Placebo	–0.03	0.70	(–1.47, 1.40)	0.9610
(bpm)	13	Placebo + Ketoconazole	1.37	0.91	(–0.49, 3.23)	0.1420
	5	Loratadine	1.09	0.76	(–0.46, 2.64)	0.1610
	13	Loratadine + Ketoconazole	4.43	1.16	(2.06, 6.80)	0.0006
Individualized	5	Placebo	0.24	0.98	(–1.76, 2.25)	0.8050
QTc (ms)	13	Placebo + Ketoconazole	7.52	1.65	(4.15, 10.89)	0.0001
	5	Loratadine	–0.52	1.81	(–4.2, 3.18)	0.7780
	13	Loratadine + Ketoconazole	10.68	2.22	(6.15, 15.21)	0.0000

** Paired t-test. Two-sided test.* n = *30.*

Table 3
Mean (%CV) steady-state pharmacokinetic parameters for ebastine and carebastine

Parameter	Ebastine day 5	Ebastine day 13	Change day 13 vs. day 5	Carebastine day 5	Carebastine day 13	Change day 13 vs. day 5
AUC (ng h^{-1} ml^{-1})	17.92 (82.0)	761.56* (36.8)	×42.5	5688.4 (29.0)	8192.2* (22.1)	×1.4
C_{max} (ng ml^{-1})	3.75 (73.2)	58.95* (37.2)	×15.7	344.62 (33.0)	384.19* (21.8)	×1.1
C_{min} (ng ml^{-1})	0.19 (98.5)	14.85* (35.3)	×78.2	145.3 (31.5)	333.8* (21.7)	×2.3
T_{max} (h)	2.42 (46.9)	4.30* (36.4)	×1.8	4.8 (37.7)	16.4* (102.8)	×3.4

**Statistically significantly different from day 5 (P < 0.05).*

Table 4
Mean (%CV) steady-state pharmacokinetic parameters for loratadine and desloratadine

Parameter	Loratadine day 5	Loratadine day 13	Change day 13 vs. day 5	Desloratadine day 5	Desloratadine day 13	Change day 13 vs. day 5
AUC (ng h^{-1} ml^{-1})	12.32 (84.3)	54.93* (58.8)	×4.5	45.93 (61.5)	89.14* (67.6)	×1.9
C_{max} (ng ml^{-1})	2.99 (88.6)	10.41* (50.1)	×3.5	3.50 (48.4)	6.37* (47.5)	×1.8
C_{min} (ng ml^{-1})	0.052 (190.3)	0.430* (82.8)	×8.3	1.00 (100)	2.21* (100)	×2.2
T_{max} (h)	1.92 (28.3)	2.28* (29.1)	×1.2	3.37 (72.4)	3.25 (47.6)	×1.0

**Statistically significantly different from day 5 ($P < 0.05$).*

8 h during combination therapy. After 8 days of coadministration with ketoconazole mean AUC, C_{max} and C_{min} increased significantly and by about 40, 16 and 60-fold, respectively, and the $t_{1/2}$ increased from 6.4 h to 87.7 h.

The pharmacokinetics of carebastine were less affected by the coadministration of ketoconazole. The mean changes observed in carebastine AUC, C_{max} and C_{min} were 1.4, 1.1 and 2.3-fold increases, respectively. Maximal carebastine concentrations were also achieved later in the presence of ketoconazole and the $t_{1/2}$ increased from 24.6 h to 80.6 h.

Maximal plasma concentrations of loratadine were achieved by 1.5–3 h during both loratadine monotherapy and the loratadine/ketoconazole combination. The mean C_{min} of loratadine was affected the most by the addition of ketoconazole, showing an increase of up to 8-fold. Mean AUC and C_{max} increased by 4.5 and 3.5-fold, respectively, and the $t_{1/2}$ marginally from 7.5 h to 9.4 h. As with ebastine, the pharmacokinetics of the primary metabolite of loratadine, desloratadine, were less affected than the parent compound. Mean AUC, C_{max} and C_{min} were approximately doubled, whereas T_{max} and $t_{1/2}$ (15 h to 13.4 h) were unchanged.

Meaningful pharmacokinetic/pharmacodynamic analysis could not be performed since the pharmacodynamic effects were not sufficiently large and could not be separated from those of ketoconazole alone. In the case of loratadine the range of plasma concentrations was also very limited and in the case of ebastine scatterplots of each QTc interval change from baseline *vs.* the corresponding plasma concentration showed an apparent plateau from low concentrations (8 ng ml^{-1}) to maximum concentrations (100 ng ml^{-1}).

Adverse event reports were relatively infrequent and there was no evidence that the increases in plasma concentrations of the antihistamines in the presence of ketoconazole resulted in alteration of the adverse event profile. The most common event was headache for both ebastine and loratadine, followed by dry skin and somnolence in the case of loratadine.

No subjects discontinued either of the studies because of ECG abnormalities. Two cardiac adverse events were reported in the ebastine study. One subject developed sporadic brief episodes of ventricular extrasystoles while receiving the placebo/ketoconazole treatment. This subject also complained of increased cough, asthenia, dyspnoea and a chest cold. Treatment was not discontinued, and the subject completed the protocol. In another subject, an unusual cardiac repolarization pattern (increased U wave, flattened T waves) was observed sporadically during the ebastine/ketoconazole phase. This subject reported no subjective complaints, and he completed the study protocol as planned. After a washout period, this subject was rechallenged with the placebo/ketoconazole treatment, during which the same ECG abnormality recurred. *Post hoc* review by the investigators also detected the same pattern on some ECGs recorded prior to administration of study medications.

In the loratadine study, some ECG abnormalities were considered beyond what would commonly be observed in healthy subjects and were recorded as adverse events. Triplets of premature ventricular beats were observed in one loratadine/ketoconazole subject and in four placebo/ketoconazole subjects. A 2.7 s sinusual pause was noted on day 13 in one subject receiving loratadine/ketoconazole.

Discussion

Ebastine alone, unlike terfenadine, has no effect on the QTc interval at therapeutic doses. However, it is metabolized by CYP3A4 and for this reason has been evaluated in comparison with loratadine, also nonarrhythmogenic, for potential drug–drug interactions and any resulting electrocardiographic effects.

Individualized α-values were used to correct the QT for changes in heart rate. The population means of the individual α-values for the ebastine and loratadine studies were 0.32 and 0.28, respectively, a finding reflected in the fact that the results obtained using Fridericia's formula ($\alpha = 0.33$) were not very different (<2 ms) from the results presented here. This is in contrast to those obtained with the Bazett ($\alpha = 0.5$) formula which seriously overcorrected the majority of the QT intervals and gave QTc values for the antihistamines plus ketoconazole some 5–6 ms higher than those using the individualized corrections. In the case of ebastine the QTcB data has appeared in a review article [25].

Despite the similarity in the population mean α-values in the two studies, as a consequence of the wide range of individual α-values the standard deviations are large. This means that the use of population mean α-values for the determination of outliers would have grossly overcorrected some QT intervals in the case of subjects with α-values less than the population mean and, potentially more important from a safety point of view, grossly undercorrected some QT intervals in those subjects with α-values greater than the population mean. The use of individual α-values to correct the QT interval obviates this problem.

Neither ebastine nor loratadine administered at maximum recommended doses caused any change in QTc following 5 days of administration. Ketoconazole alone produced a small increase in the QTc interval in both studies. When ebastine or loratadine was coadministered with ketoconazole, there was an additional increase of a few ms in the mean QTc interval above that observed with ketoconazole alone. In neither case was this increase in the QTc interval in the presence of the antihistamines statistically significant. Although the 11–12 ms combined effect of antihistamine plus ketoconazole was statistically different from baseline in each study, the clinical relevance of such small increases (in distance little more than the thickness of the tracing on the normal ECG run at 25 mm s^{-1}, where 1 mm is equivalent to 40 ms), is questionable. A more recent similar study with ebastine and ketoconazole in women, known to be more sensitive to drug effects on the QT interval [26, 27], produced a similar 12 ms increase in the individualized QTc, although ketoconazole alone was without significant effect [28].

Potentially more useful than mean central tendency values of QTc intervals in predicting arrhythmogenic risk, are the occasional extreme increases seen in some subjects. In the present studies, outlier analysis of the QTc values from each subject showed very little numerical difference between placebo, ebastine and loratadine in the presence of ketoconazole in terms of the CPMP cause for concern criteria [22]. Sporadic extreme values from a few individual electrocardiograms were associated with inappropriate measurements from defective traces. There were no clinically significant cardiac adverse events nor any clinical adverse events such as syncope or dizziness that could be suggestive of serious arrhythmias reported during any of the studies.

Our data also demonstrated that ketoconazole has a large effect on the clearance of both antihistamines. The mean increase in loratadine exposure (AUC) following the addition of ketoconazole was about 5-fold, whereas that for ebastine was about 40-fold.

Despite this difference between the magnitude of the pharmacokinetic interactions for loratadine and ebastine, the pharmacodynamic consequences were essentially the same.

Other sources [13, 29, 30] have indicated that the combination of loratadine 10 mg qd with ketoconazole 200 mg bd or this same posology of ketoconazole alone do not cause a significant change in the QTcB interval. Nevertheless the effects of ketoconazole on the pharmacokinetics of loratadine were much the same as described in the present study, implying a similar degree of metabolic inhibition. This difference from the results described here using 400 mg qd of ketoconazole has regulatory as well as potential clinical significance when ketoconazole is used as a metabolic inhibitor for drugs which are CYP3A4 substrates. It also complicates attempts to compare drug interaction effects on the QTc interval when using data from the literature.

To what extent the results of this study could have been influenced by an effect of ebastine or loratadine on the pharmacokinetics of ketoconazole is unknown, since plasma concentrations of ketoconazole were not measured. However, in a previous study with loratadine [11] and in a more recent study in women with ebastine [28] where this possibility was investigated, no such interaction was detected.

In conclusion, ketoconazole altered the pharmacokinetic profiles of both ebastine and, to a lesser extent, loratadine and itself significantly increased the QTc interval. The coadministration of ebastine or loratadine

with ketoconazole resulted in nonsignificant increases in the mean QTc intervals compared with ketoconazole given with placebo and the combined effects again reached statistical significance compared to baseline. Changes in the uncorrected QT interval following either ebastine or loratadine combined with ketoconazole were also no different from ketoconazole given with placebo.

Competing interests: None declared.

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