Effects of supratherapeutic doses of ebastine and terfenadine on the QT interval

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Aims The objective of this study was to compare the effects of high doses of ebastine with terfenadine and placebo on QTc.

Methods Thirty-two subjects were randomly assigned to four treatments (ebastine 60 mg day^{-1}, ebastine 100 mg day^{-1}, terfenadine 360 mg day^{-1}, placebo) administered for 7 days. Serial ECGs were performed at baseline and day 7 of each period. QT interval was analysed using both Bazett (QTcB) and Fridericia (QTcF) corrections.

Results Ebastine 60 mg (+3.7 ms) did not cause a statistically significant change in QTcB compared with placebo (+1.4 ms). The mean QTcB for ebastine 100 mg was increased by + 10.3 ms which was significantly greater than placebo but was significantly less ($P<0.05$) than with terfenadine 360 mg (+18.0 ms). There were no statistically significant differences in QTcF between ebastine 60 mg (−3.2 ms) or ebastine 100 mg (1.5 ms) and placebo (−2.1 ms); although terfenadine caused a 14.1 ms increase which was significantly different from the other three treatments. The increase in QTcB with ebastine most likely resulted from overcorrection of the small drug-induced increase in heart rate.

Conclusions Ebastine at doses up to five times the recommended therapeutic dose did not cause clinically relevant changes in QTc interval.

Keywords: ebastine, electrocardiographic effects, pharmacodynamics, QTc interval, terfenadine

Introduction

Some long-acting selective H_1-receptor antagonists have been associated with rare but serious cardiotoxicity. Terfenadine has been shown to cause small increases in QTc, even at the recommended dose of 60 mg twice daily in adults, while larger doses or other conditions resulting in high plasma concentrations have resulted in gross QTc prolongation that occasionally has led to seizures, ventricular fibrillation, *torsades de pointes* or death [1, 2].

Ebastine is an effective, nonsedating H_1-receptor antagonist marketed for the treatment of allergic rhinitis and urticaria. The efficacy and common adverse event profile of ebastine (10 mg once daily) is comparable with that of terfenadine (60 mg twice daily) [3]. Studies of ebastine at doses of 10 mg and 20 mg day^{-1} have shown no clinically relevant changes in QTc [3–5].

Screening drugs for QT prolongation may be useful in detecting compounds that could cause *torsades de pointes* [6]. This study was conducted to compare the effects of high doses of ebastine on QTc relative to terfenadine.

Methods

Study design

This was an investigator-blinded, four-way crossover study to compare the electrocardiographic effects of three and five times the maximum recommended dose of ebastine (60 mg and 100 mg once daily) with three times the recommended dose of terfenadine (180 mg twice daily) and placebo. Study medication was administered under direct supervision of the investigator to insure compliance. The protocol was approved by an investigational review board and subjects provided written informed consent.

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Subjects included healthy males, ages 18–40 years without any specific ECG abnormalities.

Study procedures

Subjects were randomized to each treatment (ebastine 60 mg, ebastine 100 mg, terfenadine 360 mg, and placebo) for 7 days to attain steady state, followed by a washout of 13 days. For each period, serial 12-lead electrocardiograms (ECGs) were performed on day −1 (baseline) for comparison with steady state measurements conducted on day 7 (predose, 2, 3, 4, 5, 6, 8, 12, and 23.5 h postdose).

ECG measurements

ECGs were analysed at a single site (Premier Research Worldwide, Philadelphia, PA) using a digitizer (Sigmascan, Jandel Scientific, Seattle, WA) in blinded fashion. The Sigmascan system was calibrated by measuring a series of 1 mV, 40 ms blocks from the background ECG paper (25 mm s^{-1} paper speed). After calibration, the ECG was mounted on a digitizing pad. Using a magnifier, analysts used crosshair devices to measure the RR, PR, QRS and QT intervals. QTc was calculated using the Bazett [7] [$QTcB = QT/RR^{0.5}$] and Fridericia [8] [$QTcF = QT/RR^{0.33}$] formulae. Measurements were performed across three consecutive cardiac cycles from the optimum technical portion of the lead II tracing.

Statistical methods

The primary evaluable population included all subjects who completed at least the placebo and ebastine 100 mg arms. An ANOVA for a crossover trial was used with the variables being the changes in mean QTcB (0–12 h), QTcF, uncorrected QT and heart rate (HR) from baseline to day 7. The model contained main effects for treatment, period, sequence and subject nested within sequence. *t*-tests were performed to assess effects of the treatments by forming comparisons among them. One-sided tests were utilized for ebastine 60 mg *vs* placebo, ebastine 100 mg *vs* placebo, and terfenadine *vs* placebo. Two-sided tests were used for ebastine 60 and 100 mg *vs* terfenadine. Tests of normality and homogeneity of variance were performed, as well as a check of the assumption of no carryover effect. Additionally, 95% confidence intervals for the differences between treatments were calculated.

Results

Thirty-two subjects entered the study (Table 1), of whom 31 completed at least one treatment period. The primary evaluable population included 25 subjects.

Table 1 Baseline patient demographics.

Number of patients	32
Age (years)	
Mean	27.2
Range	(19–40)
Race	
Caucasian	12
African-American	16
Oriental	1
Hispanic	3
Weight (kg)	
Mean	79.6
Range	(59–96.6)
Height (cm)	
Mean	180.4
Range	(167.6–192.4)

Pharmacodynamic results

The analysis is summarized in Table 2. Ebastine 60 mg did not cause a significant change in the mean QTcB compared with placebo. The mean QTcB for ebastine 100 mg was increased by + 10.3 ms, which was significantly greater *vs* placebo. The change in QTcB for ebastine 100 mg was significantly less ($P < 0.05$) than with terfenadine 360 mg (+18.0 ms).

There were significant increases in HR for ebastine 60 and 100 mg *vs* placebo (Table 2). Uncorrected QT was actually decreased consistent with the increased heart rate. Terfenadine resulted in a significant increase in uncorrected QT compared with placebo and ebastine. There was no change in HR with terfenadine *vs* placebo.

When QT is corrected with the Fridericia formula, there was no significant difference between placebo and ebastine 60 or 100 mg. Terfenadine caused a 13.9 msec increase in QTcF, which was significantly greater ($P < 0.0001$) than the other three treatments.

Adverse events

The most commonly reported adverse events were gastrointestinal disturbances, occurring in all treatments. No cardiac events were observed with ebastine. Three terfenadine subjects were sequestered for additional days of ECG monitoring because QTcB at day 7 increased >10%. One severe dysrhythmia (idiopathic bradycardia–tachycardia syndrome) was reported with placebo. One subject (ebastine 100 mg) discontinued because of increased GGTP.

Discussion

Allergic rhinitis is a common chronic disease frequently treated with antihistamines. While generally regarded as safe, it became apparent in the early 1990s that terfenadine

Table 2 Summary of pharmacodynamic results.

Efficacy variable	*Treatment*	n	*Baseline Mean*	*Adjusted** mean change from baseline (s.e. mean)*	*95% CI* vs *placebo*	*One-sided* P *value* vs *placebo*	*95% CI for ebastin* vs *terfenadine*	*Two-sided* P *value* vs *terfenadine*
	Placebo	25	383.8	1.4 (2.5)				
Mean QTcB	Ebastine 60 mg	24	384.8	3.7 (2.5)	[−2.86, 7.46]	0.2427	[−19.46, −9.14]	0.0000★
(ms)	Ebastine 100 mg	25	380.9	10.3 (2.5)	[3.75, 14.05]	0.0034★	[−12.86, −2.54]	0.0195★
	Terfenadine	24	382.7	18.0 (2.5)	[11.44, 21.76]	0.0000★		
	Placebo	25	381.7	−2.1 (2.1)				
Mean QTcF	Ebastine 60 mg	24	383.2	−3.2 (2.1)	[−5.43, 3.23]	0.2765	[−21.63, −12.97]	0.0001★
(ms)	Ebastine 100 mg	25	379.8	1.5 (2.1)	[−0.73, 7.93]	0.1490	[−16.93, −8.27]	0.0001★
	Terfenadine	24	381.3	14.1 (2.1)	[11.87, 20.53]	0.0001★		
	Placebo	25	378.3	−8.9 (2.4)				
Mean QT	Ebastine 60 mg	24	380.5	−17.0 (2.5)	[−13.16, −3.04]	0.9877	[−28.16, −17.84]	0.0000★
(ms)	Ebastine 100 mg	25	378.3	−15.2 (2.4)	[−11.24, −1.36]	0.9630	[−26.26, −16.14]	0.0000★
	Terfenadine	24	379.0	6.0 (2.5)	[9.84, 19.96]	0.0000★		
	Placebo	25	62.5	3.5 (1.0)				
Mean HR	Ebastine 60 mg	24	62.0	7.6 (1.0)	[2.04, 6.16]	0.0020★	[1.5, 44.56]	0.0128★
(ms)	Ebastine 100 mg	25	61.5	9.3 (1.0)	[3.74, 7.86]	0.0000★	[3.7, 14.26]	0.0003★
	Terfenadine	24	61.9	4.1 (1.0)	[−1.46, 2.66]	0.3367		

★*P* values <0.05.

★★Adjusted for imbalance of primary population in each treatment.

and astemizole were associated with an increased incidence of serious cardiac effects, such as *torsades de pointes*. These events were usually associated with overdose or recommended doses in patients with predisposing factors [9]. 'Black box' warnings were required in the US for terfenadine and astemizole regarding the potential to cause cardiac effects before they were eventually withdrawn from the market. It is therefore of importance that new antihistamines be studied for arrhythmogenic potential.

This study indicates that ebastine at three times the maximum recommended dose did not significantly alter the QTc *vs* placebo. The administration of ebastine at five times the recommended dose produced a statistically significant prolongation of QTcB *vs* placebo but not for QTcF or QT. The effects of ebastine were significantly less than terfenadine for all analyses.

It is unclear if QT should be corrected in assessing the potential to cause cardiac effects, however, QTc is commonly reported. Numerous formulae can be used to correct QT. The widely used Bazett formula has been criticized as being inaccurate in describing the relationship of QT and RR [10, 11] since it tends to undercorrect at low heart rates and overcorrects at high heart rates. A recent study suggested that the uncorrected QT and QT dispersion provided important prognostic information on cardiovascular morbidity and mortality [12]. That study also suggested that the QTcB was inappropriate as a prognostic indicator in their population.

In the present study, HR increased in both ebastine groups and the uncorrected QT decreased accordingly. The increase in QTcB for ebastine 100 mg was negated with QTcF, suggesting that over correction for heart rate may have been responsible for the change in QTcB. Terfenadine caused significant prolongation of QTc, regardless of correction formula.

In a previous study [13], retrospective analysis of the change in QTcB for terfenadine 300 mg twice daily was 42 ms. In a second study from the same publication, differences in the QTcB between terfenadine and placebo increased linearly as the dose of terfenadine was increased. The change in QTcB at a dose of 180 mg twice daily was 20–25 ms, which is consistent with this study.

In conclusion, it appears that the electrocardiographic effects of ebastine are of a different nature and magnitude than with terfenadine. While terfenadine may cause increases in QTc and dysrhythmias [1, 2], the effects of ebastine at doses up to five times those recommended for clinical use were not different from placebo.

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