Clinical and Experimental Allergy, 1999, Volume 29, Supplement 3, pages 200–205

A review of the cardiac systemic side-effects of antihistamines: ebastine

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Summary

The cardiac safety of ebastine, a long-acting, non-sedating antihistamine, has been thoroughly assessed in phase I–III clinical studies. Ebastine alone at the recommended doses of 10 mg and 20 mg has no clinically relevant effect on QTc interval in adults and in special patient populations (elderly, children or subjects with hepatic or renal impairment). Ebastine administered at 60 and 100 mg/day (3–5 times the maximum recommended dose) for 1 week had statistically significantly smaller effects (3.7 and 10.3 msec, respectively) on the QTc interval than terfenadine (18 msec) at three times the recommended dose (360 mg/day). The mean QTc interval prolongation observed with ebastine 100 mg/day was small and not clinically meaningful, although the results were statistically significant vs. placebo. The effect of ebastine 60 mg/day was not statistically different from placebo. Steady-state drug interaction studies demonstrated that the co-administration of ebastine 20 mg with ketoconazole or erythromycin produced significant increases in systemic exposure for ebastine, which were accompanied by small increases in QTc (approximately 10 msec above ketoconazole or erythromycin alone). Results from individual studies suggest that, when coadministered with ketoconazole, ebastine produces similar changes in QTc interval measurements compared to loratadine and cetirizine. Pooled data from clinical efficacy trials of ebastine 1–30 mg/day administered for 2–3 weeks showed no clinically relevant cardiac effects as assessed by serial electrocardiographs and Holter monitoring. The overall cardiac safety profile based on currently available information suggests that ebastine, like loratadine and cetirizine, has a lower potential for causing adverse cardiovascular effects than terfenadine.

Keywords: ebastine, cardiac side effects, sedation

Introduction

Shortly after the first documented cases of torsades de pointes observed with terfenadine, it was proposed that the phenomenon was associated with high serum levels of unmetabolized parent drug. The mechanism of action was believed to be blockade of cardiac potassium channels, which caused a delay in the repolarization phase of the action potential, reflected as a prolongation of the QTc interval in the electrocardiogram. This effect was not seen with the carboxylic acid metabolite, fexofenadine.

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Since then, many preclinical models have been proposed to predict the likelihood of antihistamines to induce cardiac dysrhythmias in man [1]. Whereas terfenadine and astemizole are always active in each of these models, the other non-sedating antihistamines and/or their metabolites are active in only one or two models, but not necessarily the same ones. Therefore, extrapolation of preclinical models to assess clinical risk is difficult.

In vitro, both ebastine and carebastine were without effect (3 μM) on action potentials in guinea-pig isolated papillary muscle and the human Kv1.5 channel. Carebastine (3 μM), but not ebastine, showed minor prolongation of the action potential in rabbit Purkinje fibres with the reverse being true for inhibitory effects on the HERG potassium channel.

In an *in vivo* anaesthetized guinea-pig model, using high intravenous doses, the effects seen with ebastine were much less pronounced than those observed with terfenadine, even at much lower doses [2]. Also in a conscious guinea-pig model, using a low dose of ketoconazole, with submaximal effects on the electrocardiogram, oral doses of terfenadine caused additional prolongation of the QTc interval, whereas ebastine did not [3].

In all of these guinea-pig models, carebastine, even at extremely high doses, had no effect on the QTc interval.

A different model was used to assess the ECG effects of directly infusing antihistamines (30 μg/min for 1 h) into the coronary circulation of anaesthetized dogs (mimicking the availability of drug from oral administration, but avoiding the effects of metabolism). This model demonstrated that terfenadine and astemizole, but neither ebastine nor carebastine, induced significant and progressive prolongation of the QTc interval. However, the most reliable method is the evaluation of electrocardiographic effects in man.

Clinical studies

Phase I clinical pharmacology trials were conducted to determine the cardiac safety of ebastine in healthy adults and children. Electrocardiographic recordings (ECGs), with emphasis on QTc measurement, were performed during the conduct of pharmacokinetic studies in the elderly and in subjects with hepatic or renal insufficiency, although the available data is somewhat limited. Holter monitoring was also performed in a number of these studies, and telemetry was conducted in two studies. The relationship of QTc values to plasma concentrations of ebastine and carebastine was also determined in a number of studies.

During the clinical development of ebastine, weekly ECGs were performed at baseline and at 3–5 h after ebastine administration (which approximates the time to maximum plasma concentration (t_{max}) of ebastine) in all US double-blind phase II and phase III clinical trials. The cardiac safety of ebastine was also assessed in a long-term uncontrolled study.

Cardiac safety data from clinical trials

High doses of ebastine

A four-way cross-over study of the effects of ebastine 60 and 100 mg/day, terfenadine 360 mg/day and placebo for one week was conducted. The ebastine 100 mg/day and the terfenadine treatments exhibited statistically significant mean QTc prolongation of 10.3 and 18.0 msec, respectively, compared to the placebo treatment with 1.4 msec QTc prolongation. The QTc prolongation of the ebastine 60 mg/day treatment (3.7 msec) was not significantly different from that of the placebo treatment. Compared to the terfenadine-positive control, both ebastine treatments had significantly lower QTc prolongation (Fig. 1).

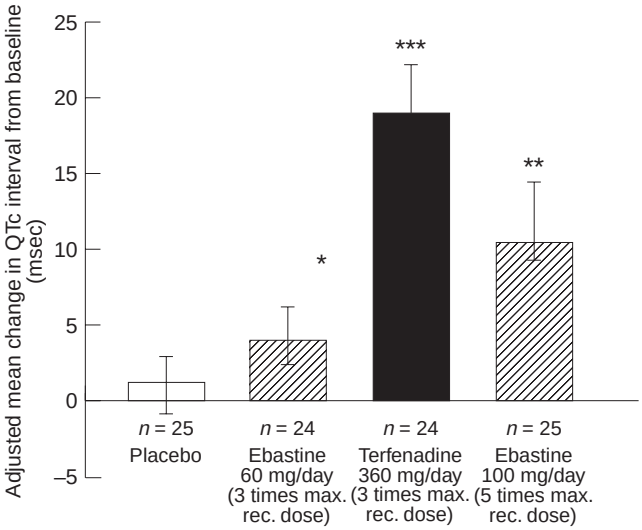

Fig. 1. Summary of adjusted mean changes in QTc intervals from baseline following administration of placebo, ebastine (60 and 100 mg/day) and terfenadine (360 mg/day) for 7 days in a four-way cross-over study of 32 healthy male volunteers. *P<0.05 vs. terfenadine only; **P<0.05 vs. terfenadine and placebo; ***P<0.05 vs. placebo and both doses of ebastine (60 and 100 mg/day).

None of the subjects had an increase in mean QTc interval >10% during treatment with ebastine, while four of 24 (17%) terfenadine recipients demonstrated a >10% increase in this parameter (Fig. 2). There were no reports of dysrhythmias or changes in ECG morphology in subjects treated with high-dose ebastine or terfenadine. Linear regression analysis demonstrated a statistically significant relationship between increasing ebastine and carebastine plasma concentrations and QTc interval changes from baseline that seemed to plateau at a low level of QTc prolongation.

Interaction with ketoconazole

Administration of a single-dose of ebastine 20 mg combined with ketoconazole 400 mg produced no clinically relevant changes in cardiac parameters in healthy male volunteers [4]. Following multiple-dose administration of ebastine 20 mg/day with ketoconazole 400 mg/day, there was a statistically significant mean QTc interval prolongation of approximately 10 msec relative to ketoconazole 400 mg/day alone (18.1 ± 2.5 vs. 8.0 ± 2.3 msec; $P = 0.0023$) [2]. No clinically relevant findings were observed during telemetry.

The majority of the ebastine- and ketoconazole-treated subjects exhibited <5% increase in mean QTc interval relative to baseline, and approximately 30% of subjects exhibited a 5–10% increase in QTc interval (Fig. 3). Similar

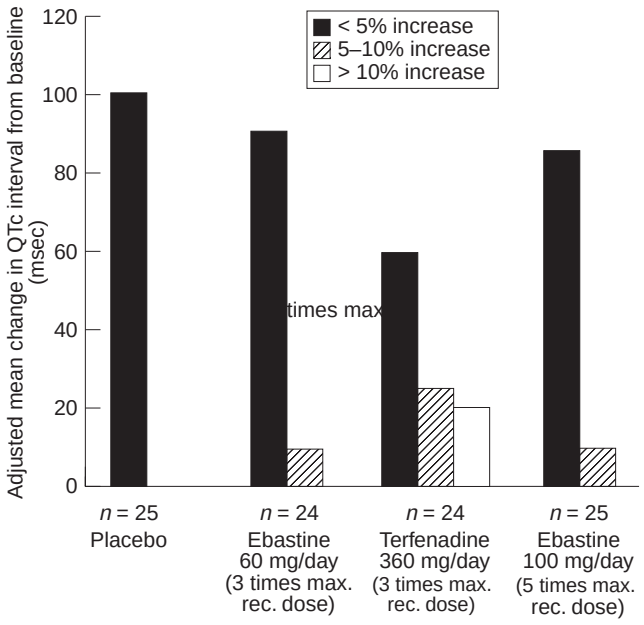

Fig. 2. Summary of the proportion of patients experiencing an increase in mean QTc interval from baseline following administration of placebo, ebastine (60 and 100 mg/day) and terfenadine (360 mg/day) for 7 days in a four-way cross-over study of 32 healthy male volunteers [4].

findings were observed in the placebo plus ketoconazole group (Fig. 3). One subject who received ebastine plus ketoconazole experienced a mean QTc interval increase >10%.

Multiple-dose administration of ketoconazole with ebastine increased the maximum plasma concentrations

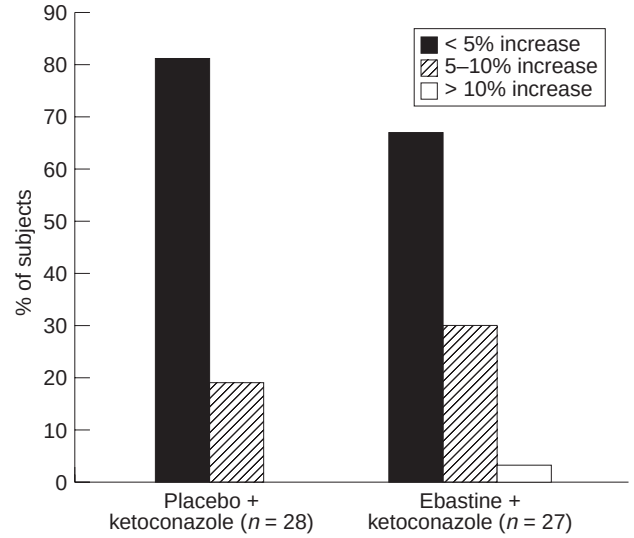

Fig. 3. Summary of the proportion of patients experiencing an increase in mean QTc interval from baseline following multiple-dose administration of placebo or ebastine 20 mg/day with ketoconazole 400 mg/day in 55 healthy male volunteers [4].

(C_{max}) of ebastine by 15-fold, minimum plasma concentrations (C_{min}) by 70-fold, and the area under the plasma concentration–time curve (AUC) by 40-fold relative to ebastine plus placebo [4]. Pooled data from the ebastine–ketoconazole interaction and high-dose ebastine studies [4] showed a positive relationship between increasing ebastine plasma concentrations and QTc interval changes that appeared to plateau at a low level of QTc prolongation [7].

In terfenadine–ketoconazole interaction studies, a strong linear correlation has been reported between plasma terfenadine concentrations and the magnitude of change on QTc interval [5,6]. In contrast to terfenadine, the results described above for ebastine indicate that the QTc interval-plasma concentration curve reaches a plateau at a low level of QTc prolongation (10 msec) despite large, progressive increases in blood concentrations of ebastine and carebastine.

Honig, *et al*. [5] reported a mean QTc interval increase of 82 msec following the coadministration of ketoconazole 200 mg twice daily with terfenadine 60 mg twice daily for seven days. Four of the six subjects did not complete the trial due to the development of abnormal morphology of the TU-complex, which suggests an increased risk for torsades de pointes. The QTc interval prolongation due to the interaction between ebastine and ketoconazole was small (18 msec) compared with that of concomitant terfenadine and ketoconazole (82 msec), and no morphological changes were observed with ebastine-ketoconazole.

It is of interest to note that the change in QTc interval observed with ebastine 20 mg plus ketoconazole 400 mg of 18 msec is comparable to that observed with cetirizine 20 mg plus ketoconazole 400 mg [8]. The combination of cetirizine and ketoconazole produced a QTc interval prolongation of 17.4 msec vs. 9.1 msec with cetirizine alone.

In another interaction study with identical methodology to that of the ebastine–ketoconazole interaction study [4], a significant QTc interval prolongation of 16.3 ± 2.52 msec was observed with coadministration of ketoconazole 400 mg and loratadine 10 mg compared with 9.6 ± 2.12 msec for ketoconazole plus placebo [4]. It should be noted that the increase in QTc for ebastine and loratadine administered with ketoconazole was similar, despite the fact that plasma concentrations of ebastine increased 40-fold while loratadine increased approximately 4-fold. Thus, although no direct comparisons have been made, these findings suggest that the increase in the QTc interval following the co-administration of ketoconazole with loratadine was comparable to those of ebastine and cetirizine.

Interaction with erythromycin

Following multiple-dose administration of erythromycin stearate 2000 mg/day with single-dose ebastine 20 mg there were no clinically relevant changes in QTc interval

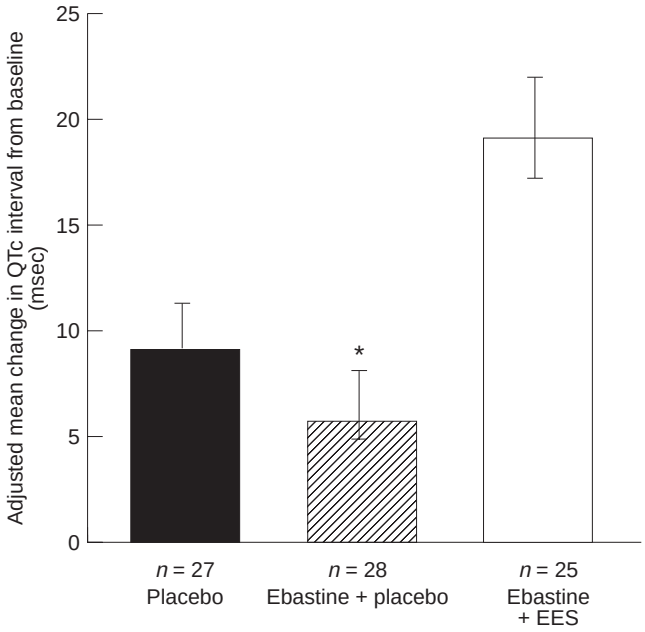

Fig. 4. Summary of adjusted mean changes in QTc intervals from baseline following administration of placebo, ebastine 20 mg/day and erythromycin ethylsuccinate (EES) 800 mg three times daily for 10 days in a three-way cross-over study of 30 healthy male volunteers. *P<0.05 vs. ebastine + EES.

or in cardiac parameters assessed by Holter monitoring and telemetry [4]. The coadministration of multiple-dose ebastine 20 mg/day with erythromycin ethylsuccinate (EES) 2400 mg/day produced a statistically significant prolongation of QTc interval of approximately 10 msec in excess of that with erythromycin alone (Fig. 4). Two (8%) subjects had >10% increases in mean QTc interval over baseline while receiving ebastine plus EES. No subject had a >10% increase in QTc interval with either drug administered alone. There were no reports of dysrhythmias or changes in ECG morphology in subjects treated with the combination of ebastine and erythromycin. No cardiac-related adverse events were detected during continuous telemetry.

Cardiac safety in special populations

The pharmacokinetics of ebastine 10 mg were similar in elderly (aged 65–82 years) and younger (aged 18–35 years) volunteers in a 10-day pharmacokinetic study [9]. There were no clinically relevant ECG changes or differences in the incidence of electrocardiographic events on Holter monitoring in either elderly or young volunteers.

In patients with moderate (creatinine clearance 30–60 mL/min/1.73 m^2; $n = 12$) and severe (creatinine clearance < 30 mL/min/1.73 m^2; $n = 10$) renal insufficiency [4,10], there were no significant differences in most carebastine pharmacokinetic parameters following single doses of ebastine 10 and 20 mg, respectively, relative to volunteers with normal renal function (creatinine clearance 85–135 mL/min/1.73 m^2; $n = 12$ and 10, respectively). Ebastine administered as a single dose produced no clinically relevant electrocardiographic effects in either group of patients with renal insufficiency, although a high degree of intra- and intersubject variability in the QTc interval was observed in patients with severe renal impairment.

In patients with histologically confirmed cirrhosis there were no significant difference in AUC or C_{max} for carebastine at a 10-mg dose compared to healthy volunteers [11]. There were no clinically relevant ECG findings between the two groups following a single dose of ebastine. Pharmacokinetic and ECG data following repeated dose administration in subjects with hepatic or renal impairment is not currently available.

In children aged 6–11 years, administration of ebastine syrup 15 mg/day for 6 days produced no clinically relevant effect on QTc interval duration relative to placebo [4]. No adverse effects were seen on ECG, Holter monitoring or telemetry.

Other pharmacokinetic/pharmacodynamic studies

Results from interaction studies demonstrate that single-dose ebastine 20 mg with theophylline [4] and single-dose ebastine 10 mg [4] and 20 mg [12] with and without food produced no clinically relevant electrocardiographic effects. Although both AUC and C_{max} values for carebastine were about 50% higher with food than without food, this is

Table 1. Summary of maximum observed QTc interval from pooled clinical trials of ebastine administered once (o.d.) or twice (b.d.) daily to adults

		No. patients (%) (maximum QTc value with ebastine)	
Treatment	No. patients	<444 msec	444–499 msec
1 mg q.d.	17	16 (94.1)	1 (5.9)
3 mg q.d.	19	19 (100.00)	0 (0.00)
10 mg q.d.	272	261 (96.0)	11 (4.0)
10 mg b.d.	74	66 (89.2)	8 (10.8)
20 mg q.d.	444	408 (91.9)	36 (8.1)
30 mg q.d.	16	14 (87.5)	2 (12.5)
Ebastine total	842	784 (93.1)	58 (6.9)
Placebo	360	339 (94.2)	21 (5.8)
Total	1202	1123 (93.4)	79 (6.6)

Table 2. Summary of the percentage change in QTc interval from baseline from pooled clinical trials of ebastine administered once (o.d.) or twice (b.d.) daily to adults

		No. patients (%) (percentage increase in QTc from baseline)	
Treatment	No. patients	< 60 msec < 15%	60–100 msec 15%–24%
1 mg q.d.	17	17 (100.0)	0 (0.0)
3 mg q.d.	19	18 (94.7)	1 (5.3)
10 mg q.d.	272	269 (98.9)	3 (1.1)
10 mg b.d.	74	73 (98.7)	1 (1.3)
20 mg q.d.	444	433 (97.5)	11 (2.5)
30 mg q.d.	16	16 (100.0)	0 (0.0)
Ebastine total	842	826 (98.0)	16 (1.9)
Placebo	360	355 (98.6)	5 (1.4)
Total	1202	1181 (98.2)	21 (1.8)

expected to be of little clinical concern as these plasma concentrations were well below those observed in the high-dose ebastine cardiac safety study [4]. Furthermore, in clinical trials, ebastine administered either with or without food has been found to be both safe and efficacious [13].

Cardiac safety data from clinical trials

Adult patients with seasonal or perennial allergic rhinitis

Pooled cardiac safety data for ebastine 1–30 mg/day were evaluated from five multicentre, placebo-controlled, double-blind studies in 1202 patients (842 ebastine and 360 placebo recipients) [14]. All patients had single ECGs performed at baseline and during the double-blind period. Holter monitoring was also performed in 226 patients.

In this analysis, generally consistent results were observed for the maximum observed QTc interval (Table 1) and the percentage change of QTc interval (Table 2) from baseline. There were no statistically significant differences between placebo and any ebastine group for mean QTc interval values and also no clinically relevant findings in any of the patients who had 24-h Holter monitoring performed. No serious adverse events were reported.

Children with seasonal allergic rhinitis

Pooled QTc data from three clinical studies [4] in 380 children aged 6–12 years demonstrated that ebastine 1–10 mg/day produced no clinically significant electrocardiographic effects (Tables 3 and 4). In these studies, a categorical threshold QTc value of 454 msec was used instead of the 444 msec value used in adults, since children have higher QTc values than adults.

Assessment of 24-h Holter monitoring data revealed no

Table 3. Summary of maximum observed QTc interval from pooled clinical trials of ebastine administered to children aged 6–12 years

		No. patients (%) (maximum QTc value with ebastine)	
Treatment	No. patients	< 454 msec	454–499 msec
1 mg	9	9 (100)	0 (0)
5 mg	186	180 (97)	6 (3.2)
10 mg	7	7 (100)	0 (0)
Ebastine total	202	197 (97.0)	6 (3.0)
Placebo	178	168 (94)	10 (6)

Table 4. Summary of the percentage change in QTc interval from baseline from pooled clinical trials of ebastine administered to children aged 6–12 years

		No. patients (%) (percentage increase in QTc from baseline)	
Treatment	No. patients	< 15%	> 15%–25%
1 mg	9	9 (100)	0 (0)
5 mg	186	179 (96)	7 (4)
10 mg	7	7 (100)	0 (0)
Placebo	178	177 (99)	1 (1)

notable findings except for one patient who experienced second-degree AV block following ebastine 5 mg. This patient was withdrawn per study protocol; follow-up Holter monitoring 6 days later did not show any findings.

Long-term clinical trial

The electrocardiographic effects of up to 4 months' treatment with ebastine 10 or 20 mg were also assessed in an open-label study in adults [4]. No patient had an increase in QTc interval >20% or a maximum QTc interval prolongation ≥500 msec. One patient had premature ventricular contractions, other premature beats, and trigeminy and discontinued the study medication; however, this patient had a history of rare palpitations and flutter [4].

Conclusions

The cardiac safety of ebastine has been extensively studied and characterized. Ebastine has no clinically relevant effect on QTc interval at the recommended doses of 10 mg and 20 mg administered once daily to patients with allergic rhinitis (12 years and older), healthy volunteers or to special populations (elderly, subjects with renal or hepatic insufficiency, and children 6–12 years of age). Even when coadministered with ketoconazole or erythromycin or when given at high doses, the total QTc effect is clinically not significant. In conclusion, the overall cardiac safety profile of ebastine is very favourable. Based on currently available information, the findings suggests that ebastine, like loratadine and cetirizine, has a lower potential for causing ventricular repolarization changes than terfenadine or astemizole.

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