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Effects of terfenadine, astemizole and epinastine on electrocardiogram in conscious cynomolgus monkeys

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Abstract

We examined the effects of non-sedative histamine H_1 receptor antagonists on the electrocardiogram (ECG) in conscious cynomolgus monkeys. Terfenadine (3 mg kg^{-1} h^{-1}, i.v.) and astemizole (0.3 and 1 mg kg^{-1} h^{-1}, i.v.) caused significant time-dependent increases in the QT interval and QTc Bazett (QTc). However, normal ECG forms were found during a 60-min infusion of epinastine (3 mg kg^{-1} h^{-1}, i.v.). A higher dose of epinastine (10 mg kg^{-1} h^{-1}, i.v.) increased the QTc and PR interval only 5 min after the start of the infusion. The minimum plasma concentrations of terfenadine, astemizole and epinastine which caused QTc prolongation were 85, 35 and over than 3600 ng/ml, respectively. These drugs did not alter the PQ and QRS intervals and did not cause arrhythmia or atrioventricular block. Our results are consistent with the clinical observation that prolongation of QTc is caused by terfenadine and astemizole but not by epinastine. Thus, measurement of QTc in cynomolgus monkey appears to be a useful approach for evaluating the potential cardiotoxicity of histamine H_1 receptor antagonists.

Keywords: Histamine H_1 receptor antagonist; Terfenadine; Astemizole; Epinastine; Cynomolgus monkey; ECG (electrocardiogram)

1. Introduction

The classical histamine H_1 receptor antagonists induce excessive clinical sedation because they penetrate the blood-brain barrier, which limits their clinical usefulness. Accordingly, a new generation of histamine H_1 receptor antagonists, such as terfenadine and astemizole, that lack excessive sedative properties was developed (Conti, 1994; Vella and Floridia, 1998).

However, these newer agents can prolong the QT interval which may culminate, in rare instances, in torsades de pointes, a life-threatening form of polymorphic ventricular tachycardia (Botstein, 1993; Koh et al., 1994; Smith, 1994; Tran, 1994; Woosley, 1996). The arrhythmogenic effects of terfenadine are believed to be associated with the unchanged form of this drug (Salata et al., 1995; Roy et al., 1996; Vorperian et al., 1996). However, the arrhythmogenic effects of astemizole are associated with both astemizole and its main metabolite (desmethylastemizole) (Vorperian et al., 1996). Since these agents are metabolized by hepatic microsomal cytochrome *P*450 (CYP) 3A4, concomitantly used drugs that inhibit this enzyme (e.g., macrolide antibiotics, triazole antifugal drugs) may lead to such high plasma concentrations of terfenadine and astemizole that there may be an increased risk of serious cardiac arrhythmia (Garteiz et al., 1982; Zimmermann et al., 1992; Botstein, 1993; Hsieh et al., 1996; Tsai et al., 1997; Albengres et al., 1998; Vella and Floridia, 1998).

The decreased lipophilicity and the bulk of the substituting group attached to the tertiary amine of the histamine H_1 receptor antagonist molecule seem to be two crucial parameters in determining the cardiotoxic capacity of antihistaminic molecules (Zhang, 1997). In fact, both astemizole and terfenadine have less polar but bulkier phenyl

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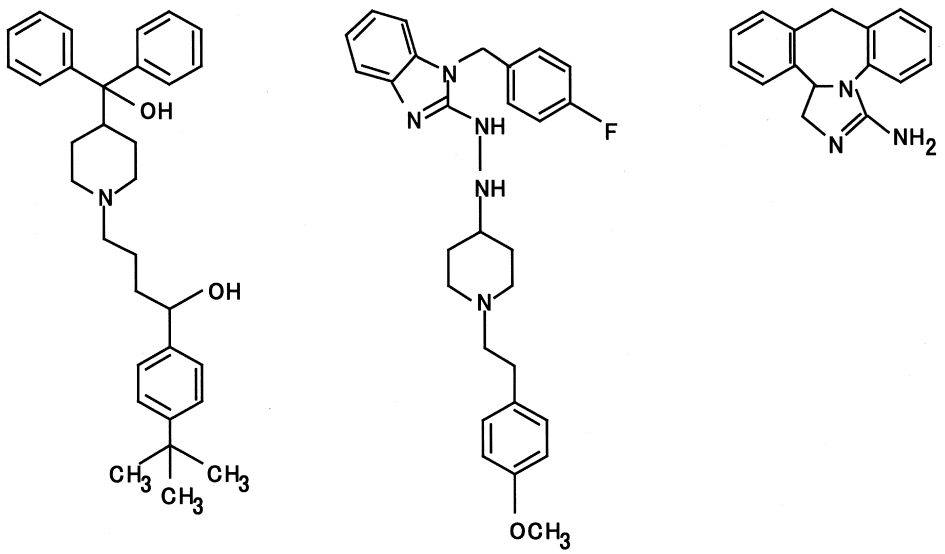

Terfenadine Astemizole Epinastine

Fig. 1. Chemical structures of terfenadine, astemizole and epinastine.

rings in the side chain than epinastine (Fig. 1). Epinastine is a recently developed non-sedative histamine H_1 receptor antagonist (Misawa et al., 1991; Kamei et al., 1992; Tasaka et al., 1994). Because epinastine has a polar and smaller substitution on the nitrogen group (Fig. 1), it is expected that the cardiotoxicity of epinastine will be weaker than that of astemizole and terfenadine.

Arrhythmogenic effects of a new generation of histamine H_1 receptor antagonists (terfenadine and astemizole) have been reported in conscious animals (Gras et al., 1996; Hey et al., 1996). However, the comparative effects of terfenadine, astemizole and epinastine on electrocardiogram (ECG) parameters including QTc in conscious animals have not been reported. Therefore, we determined the effects of these compounds on the ECG of conscious cynomolgus monkeys.

2. Materials and methods

2.1. Chemicals

Terfenadine and astemizole were obtained from Sigma (St. Louis, MO, USA). Epinastine hydrochloride was synthesized by Boehringer Ingelheim Pharm K.G., Germany.

2.2. Animal care and use

All experimental procedures were approved by the Animal Care Committee of the Nippon Boehringer Ingelheim, and were based on the ''Guide for the Care and Use of Laboratory Animals'' of the National Institutes of Health (NIH, Bethesda, MD, USA).

2.3. Electrophysiological experiments

Five male cynomolgus monkeys weighing 4.0 to 6.0 kg supplied by Keari, were used in this experiment. The ECG was recorded with the monkey in the sitting position on a monkey chair. Before administration, the monkeys were trained to sit down on a monkey chair for 90 min once a day for 7 days and to accept the procedure of ECG recording. A disposable patch electrode for ECG monitoring (Vitrode, Nihon Koden, Japan) was positioned on the animal using an ECG lead II pattern (left leg, right arm and one reference electrode). The analogue ECG waveforms were displayed and recorded by MP 100WS (duration 10 s, sampling frequency 1000 Hz, filter cut-off 50 Hz) (BIOPAC System, USA). The waveforms were analyzed to determine the ECG parameters, QT, PR, QRS, PQ and RR intervals (heart rate) automatically using an MP/ECG2 (Physio-Tech, Tokyo, Japan). The corrected QT interval (QTc) was also calculated automatically using the preceding RR interval according to Bazett's formula (Bazett, 1920).

Terfenadine, astemizole and epinastine were dissolved in 10% dimethylsulfoxide and 0.2% L-lactic acid (vehicle). Terfenadine (1 and 3 mg kg^{-1} h^{-1}, i.v.), astemizole (0.3 and 1 mg kg^{-1} h^{-1}, i.v.), epinastine hydrochloride (3 and 10 mg kg^{-1} h^{-1}, i.v.), or vehicle was infused into the left saphenous vein at a rate of 2 ml kg^{-1} h^{-1} for 60 min by means of an infusion pump (Terumo, Japan, STC-523).

The ECG was recorded 1 min before the start of the infusion and every minute during the first 10 min and then

15, 20, 30, 40, 50 and 60 min after the start of the infusion.

2.4. Pharmacokinetic experiments

Pharmacokinetic studies were performed in the same animals used for the ECG experiments. Blood samples before and after drug administration were drawn from the right cephalic vein at 5, 15, 30 and 60 min for the measurement of plasma concentrations of epinastine, terfenadine, and astemizole plus desmethylastemizole. Plasma (500 μl) was separated by centrifugation at 3000 r.p.m. and stored at −20°C until analysis. Drug concentrations were determined by means of high-performance liquid chromatography (HPLC) with an ultraviolet detector (astemizole, epinastine) and by HPLC with a fluorescence detector (terfenadine).

2.5. Statistics

The experiments were performed in a crossover design. Values are expressed as means ± S.E.M. for five animals in each treatment. Significant differences ($P < 0.05$, 0.01) between the effects of treatments and vehicle were tested for significance by One-way analysis of variance (ANOVA) and Dunnett's *t*-paired test. The correlation between plasma concentration and change in QTc was calculated using Pearson's correlation test.

3. Results

3.1. Effects of terfenadine, astemizole and epinastine on ECG in conscious cynomolgus monkeys

Terfenadine (1 mg kg^{-1} h^{-1}, i.v.) caused slight increases in the QT interval and QTc. These effects attained significance only 50 min post-infusion (Fig. 2a and b). Terfenadine (3 mg kg^{-1} h^{-1}, i.v.) caused significant time-dependent increases in the QT interval (30–40 ms) and QTc (0.02–0.04 unit) (Fig. 2a and b). Astemizole (0.3 and 1 mg kg^{-1} h^{-1}, i.v.) also caused significant increases in the QT interval (10–40 ms) and QTc (0.02–0.06 unit) in a time-dependent manner (Fig. 3a and b). Epinastine (3 mg kg^{-1} h^{-1}, i.v.) did not alter the heart rate or PR, QRS, QT intervals or QTc. Normal ECG forms were recorded during infusion of epinastine for 60 min (data not shown). A higher dose of epinastine (10 mg kg^{-1} h^{-1}, i.v.) caused an increase in the QTc (Fig. 4b) and slight decrease in the PR interval (increase in heart rate), which attained significance only 5 min after the start of the infusion (data not shown). However, these effects were not time-dependent, and disappeared 60 min after the start of the infusion (Fig. 4a and b). These drugs (terfenadine, astemizole and epinastine) did not alter other parameters (PQ interval and QRS interval) and did not cause arrhythmia (ectopic beat or fibrillation) or atrioventricular block. Special behavior

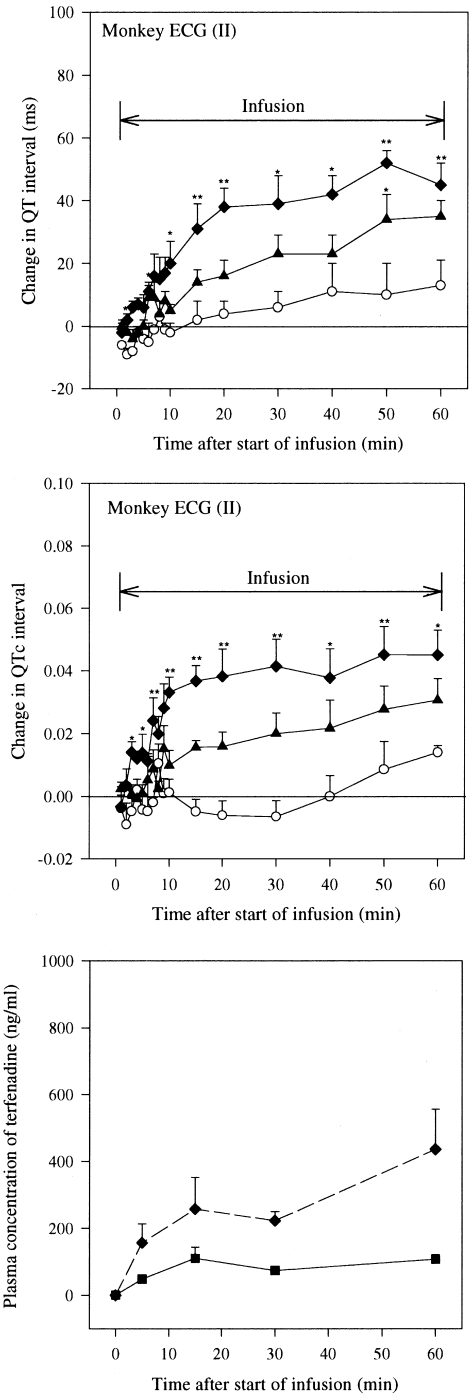

Fig. 2. Effects of intravenous administration of terfenadine 1 mg kg^{-1} h^{-1} (■), terfenadine 3 mg kg^{-1} h^{-1} (♦) and vehicle (○) on (a) QT interval, (b) QTc, and (c) plasma concentration of terfenadine in conscious cynomolgus monkeys. Values represent means ± S.E.M. of five experiments; $^{*}P < 0.05$, $^{**}P < 0.01$ compared with vehicle.

(sedation or excitation) and gastrointestinal reactions (retching, vomiting or defecation) were not observed.

3.2. Plasma concentrations of terfenadine, astemizole plus desmethylastemizole, and epinastine

Fexofenadine, the main metabolite of terfenadine, does not appear to have cardiotoxic effects (Roy et al., 1996). In

contrast, both astemizole and its metabolite (desmethylastemizole) have cardiotoxic effects in isolated rabbit myocytes (Vorperian et al., 1996). Only the unchanged form

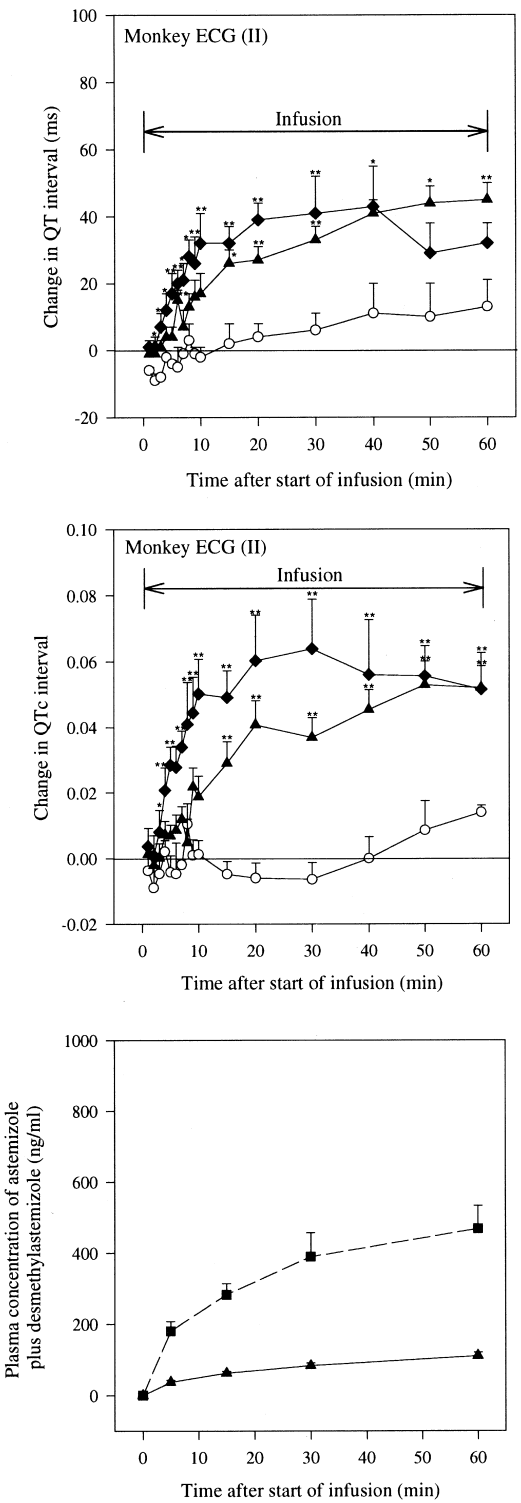

Fig. 3. Effects of intravenous administration of astemizole 0.3 mg kg^{-1} h^{-1} (▲), astemizole 1 mg kg^{-1} h^{-1} (■) and vehicle (○) on (a) QT interval, (b) QTc, and (c) plasma concentration of astemizole in conscious cynomolgus monkeys. Values represent means ± S.E.M. of five experiments; $^{*}P < 0.05$, $^{**}P < 0.01$ compared with vehicle.

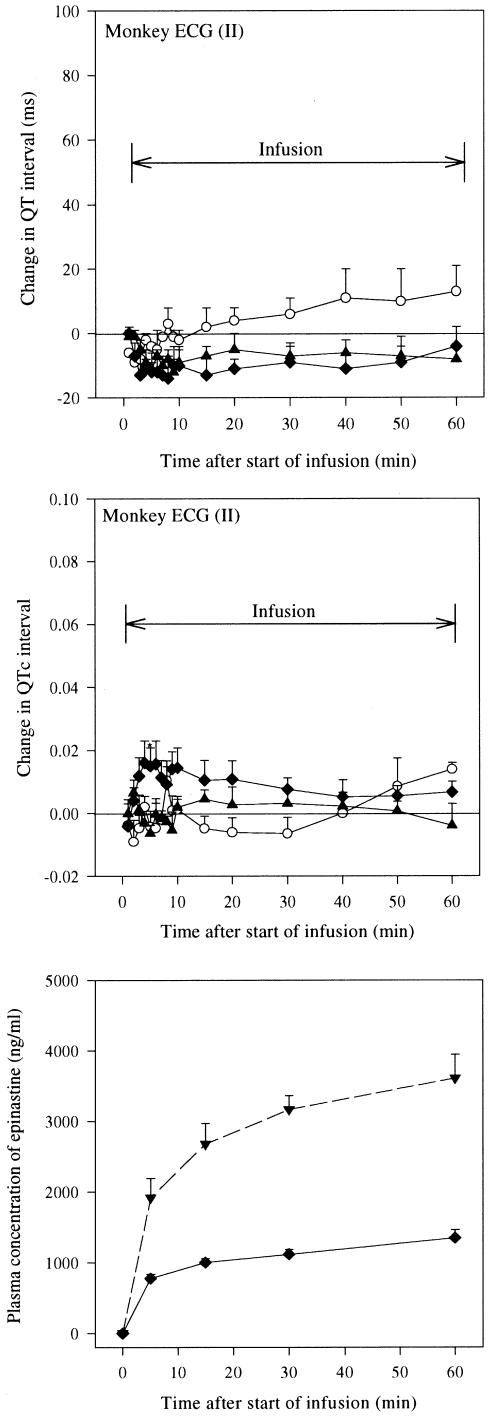

Fig. 4. Effects of intravenous administration of epinastine 3 mg kg^{-1} h^{-1} (◆), epinastine 10 mg kg^{-1} h^{-1} (▼) and vehicle (○) on (a) QT interval, (b) QTc, and (c) plasma concentration of epinastine in conscious cynomolgus monkeys. Values represent means ± S.E.M. of five experiments; $^{*}P < 0.05$ compared with vehicle.

of epinastine is found in plasma after oral administration to humans. Therefore, we measured the plasma concentrations of terfenadine, astemizole plus desmethylastemizole, and epinastine.

Plasma concentrations of terfenadine in conscious monkeys following intravenous administration of doses of

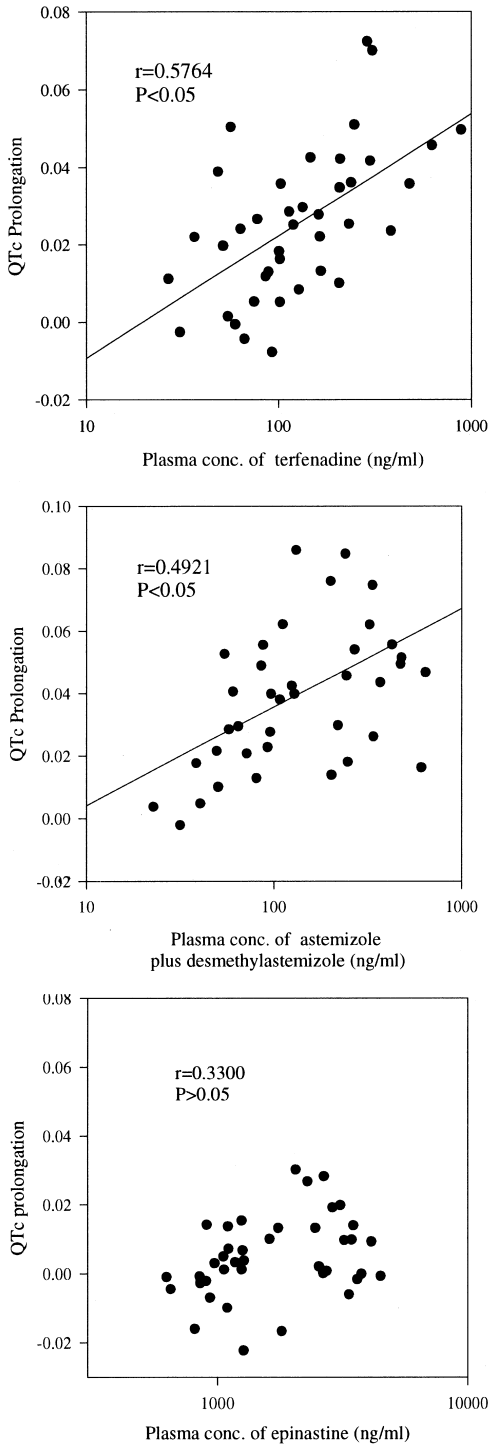

Fig. 5. Correlation between plasma concentrations of drugs and change in QTc (a) terfenadine (b) astemizole plus desmethylastemizole, and (c) epinastine.

1 and 3 mg kg^{-1} h^{-1}, i.v. (Fig. 2c) were 107 ± 14 and 436 ± 120 ng/ml 60 min after the start of the infusion. Plasma concentrations of astemizole plus desmethylastemizole at doses of 0.3 and 1 mg kg^{-1} h^{-1}, i.v. (Fig. 3c) were 110 ± 9 and 468 ± 65 ng/ml 60 min after the start of the infusion. Plasma concentrations of epinastine at doses of 3 and 10 mg kg^{-1} h^{-1}, i.v. (Fig. 4c) were 1349 ± 115 and 3609 ± 340 ng/ml 60 min after the start of the infusion.

3.3. Correlation between changes in QTc and plasma concentrations

We investigated the correlations between changes in QTc and the plasma concentrations of terfenadine, astemizole plus desmethylastemizole and epinastine, in order to determine the minimal concentration producing QTc prolongation. There were weak but significant correlations between plasma concentrations of terfenadine ($r = 0.5764$, $P < 0.05$) and astemizole plus desmethylastemizole ($r = 0.4921$, $P < 0.05$) and QTc prolongation (Fig. 5a and b). In the experiments with terfenadine and astemizole, there was a significant difference between the effect of vehicle and the drugs on QTc prolongation, with the prolongation of the QTc reaching about 0.02 unit. Therefore, we tried to determine the minimum concentrations of terfenadine and astemizole that produced QTc prolongation of 0.02 unit. The minimum concentrations of terfenadine and astemizole plus desmethylastemizole producing a QTc prolongation of 0.02 unit, calculated by using correlation fitting, were 85 and 35 ng/ml, respectively.

4. Discussion

Terfenadine is mainly transformed to fexofenadine, which is also a potent histamine H_1 receptor antagonist, but has little cardiotoxic effect (Salata et al., 1995; Roy et al., 1996). Astemizole is also metabolized to desmethylastemizole by the liver. Astemizole and desmethylastemizole both have potent histamine H_1 antagonistic and cardiotoxic effects (Vorperian et al., 1996). Drugs that interfere with hepatic metabolism (e.g., ketoconazole and macrolide antibiotics) may cause high plasma concentrations of the unchanged form of terfenadine or astemizole, which may lead to clinically relevant cardiotoxicity. Epinastine is only minimally metabolized, and the unchanged form of epinastine is found in plasma after oral administration. Therefore, hepatic metabolic inhibitors probably do not affect plasma concentrations of the unchanged form of epinastine (Kishimoto et al., 1997).

Terfenadine, astemizole and epinastine were infused intravenously to reduce the first-pass effect by the liver, since we wished to determine the cardiotoxicity of the unchanged forms of drugs and/or those of metabolites. We also determined the correlation between the plasma concentrations and cardiotoxicity (QTc prolongation) of these drugs.

The maximum plasma concentrations (C_{max}) of terfenadine and astemizole, measured in humans after a single oral dose (60 and 10 mg, respectively), which show a pronounced effect against allergic disease are 1.3 and

1 ng/ml, respectively (Garteiz et al., 1982; Estelle and Simons, 1990). In comparison, the minimum plasma concentrations of terfenadine and astemizole which cause QTc prolongation were 85 and 35 ng/ml in cynomolgus monkeys, respectively. Therefore, the plasma concentrations of astemizole and terfenadine which cause QTc prolongation in this model were 65× and 35× higher than the therapeutic plasma concentration in humans.

The plasma concentration of terfenadine (85 ng/ml) that prolonged the QTc in cynomolgus monkeys was of the same order of magnitude as the plasma concentrations of terfenadine found in humans after administration of a clinical dose of 60 mg p.o. in combination with CYP 3A4 inhibitors such as itraconazole (21 ng/ml; Honig et al., 1993a), ketoconazole (81 ng/ml; Honig et al., 1993b) and erythromycin (34 ng/ml; Honig et al., 1992). The plasma concentrations of astemizole and desmethylastemizole which produced QTc prolongation (35 ng/ml) in the present study were five-fold higher than those of astemizole and desmethylastemizole (7.7 ng/ml; Vorperian et al., 1996) found in humans treated with clinical doses of 10 mg, p.o. under conditions of decreased metabolic activity. The maximum concentration (C_{max}) of epinastine in humans after a single oral dose of 10 mg is approximately 36 ng/ml. By comparison, the plasma concentration of epinastine obtained after an intravenous infusion of 10 mg kg^{-1} h^{-1} was 3609 ± 760 ng/ml 60 min after the start of the infusion. At 60 min, epinastine affected neither the QTc nor the QT interval. Therefore, the plasma concentration of epinastine achieved in this cynomolgus monkey model was at least 100 times higher than that achieved clinically in humans. It is reported that epinastine is only minimally metabolized in the liver and that the plasma concentration of epinastine may not be affected by metabolic inhibitors (Kishimoto et al., 1997). These results suggest that epinastine might be superior to terfenadine and astemizole in terms of adverse ECG effects even when metabolic activity is decreased.

A prolongation of the QTc, but not the QT interval, was observed 5 min after the start of epinastine infusion (10 mg kg^{-1} h^{-1}). It may be due to a decrease in the RR interval, which was also previously reported in dogs (Ohara et al., 1992) and rats (Ohtani et al., 1997). The tachycardiac effect of epinastine may be provided by its α_1-adrenoceptor antagonistic action (Ohara et al., 1992).

In humans, the QT prolonging effect of terfenadine was greater than that of astemizole, especially after oral administration with a liver metabolic inhibitor (Zechnich et al., 1994). The findings of the present study are consistent with these clinical observations, suggesting that our cynomolgus monkey model is useful for examining QTc prolongation by histamine H_1 receptor antagonists.

Since $I_{K(Vr)}$ contributes significantly to action potential repolarization, inhibition of $I_{K(Vr)}$ prolongs action potential duration. Human *ether-a-go-go*-related gene (HERG) channels expressed in *Xenopus* oocytes have electrophysiological properties identical to the cardiac conductance $I_{K(Vr)}$ (Roy et al., 1996). In this preparation, terfenadine and astemizole blocked the HERG channels expressed in *Xenopus* oocytes, whereas epinastine had little effect on that current (Chachin et al., 1998). The IC_{50} values for terfenadine, astemizole and epinastine were 431 nM, 69 nM, and >1000 μM, respectively. These findings are also consistent with our results for cynomolgus monkeys.

In conclusion, our findings are consistent with the clinical adverse effect (QTc prolongation) of histamine H_1 receptor antagonists, suggesting that our method with conscious cynomolgus monkeys is useful for examining QTc prolongation by histamine H_1 receptor antagonists.

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