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Research Article

# Effects of Antihistamines, Ebastine and Terfenadine, on Electrocardiogram in Conscious Dogs and Cats

**Yoshihide Kii,[1]* Katsuyoshi Nakatsuji,[1] Isamu Nose,[1] Masafumi Yabuuchi,[1] Michiaki Matsuda,[2] and Tsugutaka Ito[1]**

*[1]Safety Research Laboratories, Dainippon Pharmaceutical Co. Ltd., Osaka, Japan*
*[2]Pharmacokinetics and Physico-Chemical Property Research Laboratories, Dainippon Pharmaceutical Co. Ltd., Osaka, Japan*

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**ABSTRACT** The purpose of this study was to evaluate the effects of ebastine and terfenadine on the electrocardiogram of conscious dogs and cats. In dogs, terfenadine at oral doses of 30 mg/kg twice a day for 7 days prolonged the electrocardiographic QT interval and the corrected QT (QTc) interval on the seventh day, whereas the drug did not affect these parameters on the first day. Plasma concentrations of terfenadine and its active metabolite, fexofenadine, reached 306 and 8,541 ng/mL, respectively, on the seventh day. Ebastine at oral doses of 30 and 100 mg/kg once a day for 7 days was without effect on the QT and QTc intervals, whereas the drug slightly shortened the RR interval. On the seventh day following the dose of 100 mg/kg, plasma concentrations of ebastine and its active metabolite, carebastine, reached 36 and 1,939 ng/mL, respectively. In conscious cats, terfenadine at oral doses of 30 mg/kg twice a day for 7 days prolonged the QT and QTc intervals, QRS duration, JT and the corrected JT intervals. Unexpectedly, terfenadine induced ventricular tachyarrhythmia and premature beats. On the other hand, ebastine at oral doses of 100 mg/kg once a day for 7 days was without effect on the electrocardiographic parameters in cats. These results suggest that the electrocardiographic changes indicative of the proarrhythmic potential of terfenadine can be evaluated in conscious dogs and especially in conscious cats by repeated oral administration, and that ebastine does not induce such changes. 58:209–217, 2003. 

**Key words:** electrocardiogram; terfenadine; ebastine; dogs; cats

## INTRODUCTION

Several noncardiac drugs, such as antipsychotics, antidepressants, antihistamines, and quinolones, have been shown to prolong the QT intervals on the electrocardiogram (ECG) and sometimes to induce life-threatening ventricular tachyarrhythmias (VTs), such as torsades de pointes (TdP), in humans [De Ponti et al., 2000]. The potential to induce VTs has been evaluated frequently using anesthetized animal models. However, it has been reported that some anesthetics by themselves prolong the QT intervals and/or the corrected QT (QTc) intervals in dogs [Hammond et al., 2001] and that the apparent proarrhythmic potential of drugs in anesthetized dogs differs according to the anesthetic agents used [Weissenburger et al., 2000; Yamamoto et al., 2001]. In addition, in anesthetized animals, test drugs are generally administered intravenously, whereas most noncardiac drugs that induce QT-prolongation and TdP clinically are orally administered in humans.

*Correspondence to: Yoshihide Kii, Safety Research Laboratories, Dainippon Pharmaceutical Co. Ltd., 33-94 Enoki, Suita/Osaka 564-0053, Japan.
E-mail: yoshihide-kii@dainippon-pharm.co.jp

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Therefore, it is more logical to evaluate the proarrhythmic potential of drugs in conscious animals using the clinical route of administration.

Antihistamines have been widely used for the treatment of chronic urticaria and allergic rhinitis. However, the second-generation antihistamines, astemizole and terfenadine, have been reported to induce excess prolongation of QT intervals and TdP in human when the plasma concentration of parent drug increases [De Ponti et al., 2000; Dresser et al., 2000]. These cardiac adverse effects have been suggested to be mainly mediated through the inhibition of the rapid activating delayed rectifier K currents (Ikr), as demonstrated in isolated ventricular myocytes [Salata et al., 1995; Ducic et al., 1997], and the human ether-á-go-go related gene (HERG) current [Roy et al., 1996; Suessbrich et al., 1996]. Ebastine is also positioned as a second-generation antihistamine and has a potent and long-lasting block of $H_1$-receptor [Llupiá et al., 1992; Yakuo et al., 1994]. Ebastine and its active metabolite, carebastine, have been shown to have no effect on the action potential duration in isolated guinea pig papillary muscles [Kii et al., 1996] or isolated rabbit Purkinje fibers [Cavero et al., 1999]. In addition, it has been reported that ebastine at intravenous doses of 0.1–3 mg/kg does not affect either the RT intervals in anesthetized dogs, which is the distance from the largest deflection of R wave to a peak of T wave in ECG [Nakamura et al., 1998], or the QTc intervals in anesthetized guinea pigs [Llenas et al., 1999]. Direct infusion of ebastine (30 μg/min for 60 min) into the coronary circulation of anesthetized dogs was, in contrast to terfenadine, also without effect on the QTc intervals [Gras et al., 1996]. On the other hand, it has been reported that ebastine inhibits $I_{kr}$ in guinea pig isolated ventricular myocytes and HERG currents [Ko et al., 1997] and prolongs the QTc intervals in anesthetized guinea pigs [Hey et al., 1996], although the concentrations and doses of ebastine causing these cardiac effects were extremely high [Nakamura et al., 1998; Ten Elick et al., 2001].

The purpose of this study was to evaluate the effects of repeated oral administrations of ebastine and terfenadine on the electrocardiogram of conscious dogs and cats in terms of proarrhythmic signals. The plasma concentrations of these antihistamines and their metabolites in conscious dogs were also measured.

## MATERIALS AND METHODS

### Animals

The experiments were carried out in accordance with the Guide for the Care and Use of Animals defined by the Internal Committee of Experimental Animals in Dainippon Pharmaceutical Co. Ltd., under the approved protocols. Animals used in the present study were as follows: male beagle dogs (Kasho Co. Ltd., Tokyo, Japan) weighing 11.2–13.6 kg, and male and female Ico Fec Eur cats weighing 2.6–4.4 kg (IFFA CREDO, Arbresle, France). The animals were housed in a room lit for 12 h per day and kept at a room temperature of $23 \pm 2^{\circ}C$ and humidity of $55 \pm 5\%$. Food was given once a day, and water was continuously available.

### Compounds

Ebastine and carebastine were supplied by Almirall Prodesfarma (Barcelona, Spain). Terfenadine was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). The main active metabolite of terfenadine, fexofenadine hydrochloride, was extracted from the commercial source (Allegra, Aventis Pharma S.A., Romainville, France) in our Exploratory Research Laboratories. Ebastine and terfenadine were suspended in 0.5% tragacanth gum solution.

It is well known that drugs with arrhythmogenic potential often cause ventricular arrhythmia when overdosed or administered concomitant with metabolic inhibitors. In this study, ebastine and terfenadine were orally administered at doses that were more than 10 times the effective doses in rats and guinea pigs [Yakuo et al., 1994]. The volumes of oral administration were set at 2 mL/kg. It has been reported that ebastine given orally at a dose of 3 mg/kg inhibits homologous passive cutaneous anaphylaxis (PCA) in guinea pigs 24 h after administration, whereas terfenadine at 30 mg/kg p.o. does not inhibit PCA 6 h after administration [Yakuo et al., 1994]. Thus, ebastine and terfenadine were orally administered once and twice a day, respectively.

### ECG Measurement

The surface lead II ECG was measured from the limbs using skin patches and recorded using an ECG recorder (ECG-6601, Nihon Kohden, Tokyo, Japan). In dogs, each animal was partially restrained in a standing position throughout the experiments using a body belt fixed to a solid frame. In cats, each animal was maintained in the prone position on a stereotaxic apparatus at each time point measuring ECG. In order to acclimate to the experimental conditions, all animals were trained at least twice under the ECG measurement conditions before the experiments. ECG was measured for 10 sec more than three times at each time point, and the signals were stored on a hard disk before being automatically averaged by an ECG analyzer (Genius ver 2.19, Medical Research Equipment Co., Tokyo, Japan). With all data averaged, a skillful

observer manually measured QT intervals and QRS duration on a computer display. The QT intervals and QRS duration were measured from the onset of the Q waves to the end of the T waves and from the onset of the Q waves to the end of the S waves, respectively. The end of the T wave was determined by its electrical potential measured by the ECG analyzer: when the electrical potential at a point was the same as that at the start of the P wave, the point was defined as the end of the T wave. The same handlers for each animal were used to obtain the ECG.

It has been reported that the corrected QT (QTc) intervals calculated by Bazett's formula ($QTc = QT/(RR\ intervals)^{\frac{1}{2}}$ [Bazett, 1918]) is unlikely to be suitable for dogs [Hammond et al., 2001]. Matsunaga et al. [1997] proposed a one-parameter logarithmic formula ($QTc = \log 600 \times QT/\log RR$) for correcting the QT intervals, exhibiting a good correction over a wide range of RR intervals. Therefore, in this study, QTc intervals in conscious dogs were calculated by the one-parameter logarithmic formula.

Although the QT intervals in conscious cats are also greatly influenced by heart rate [Ware and Christensen, 1999], a suitable formula for calculation of the corrected QT intervals in conscious cats has not been demonstrated yet. In order to compare the effects of the antihistamines on QTc intervals in dogs with those in cats, the QTc intervals in conscious cats were also calculated by the logarithmic formula. When the QRS duration was significantly prolonged, the JT interval and the corrected JT (JTc) interval were calculated: $JT = QT - QRS$ and $JTc = \log 600 \times (JT/\log RR)$.

### Effects of Repeated Administration of Ebastine and Terfenadine on ECG

In the first study, the effects of repeated oral administrations of ebastine and terfenadine on the ECG were examined in conscious dogs. The animals were divided randomly into four groups ($n = 4$): vehicle, ebastine 30 and 100 mg/kg, and terfenadine 30 mg/kg groups. Vehicle or terfenadine (30 mg/kg) was administered twice a day (9–11 a.m. and 5–6 p.m.) from the first to the sixth day. On the seventh day, vehicle or terfenadine was administered only once (9–11 a.m.). Ebastine was administered once a day (9–11 a.m.) for 7 days.

In the second study, the effects of repeated oral administration of ebastine and terfenadine on the ECG were examined in conscious cats. The animals were divided randomly into three groups ($n = 4$): vehicle (2 male and 2 female cats), ebastine (3 males and 1 female), and terfenadine (4 males) groups. Vehicle or terfenadine (30 mg/kg) was administered twice a day (9–11 a.m. and 5–6 p.m.) from the first to the sixth day. On the seventh day, vehicle or terfenadine was administered only once (9–11 a.m.). Ebastine (100 mg/kg) was administered only once a day (9–11 a.m.) for 7 days.

In the terfenadine-treated group, one male cat showed VT on ECG on the sixth day of repeated oral administration. After resuscitation by artificial respiration, the cat was orally administered 30 mg/kg of terfenadine on the next (seventh) day and the ECG was measured.

### Determination of Plasma Concentrations of Ebastine, Terfenadine, and Their Metabolites in Conscious Dogs

In the first study, blood samples were obtained by venipuncture of a forelimb at 0, 1, 2, 3, 5, and 7 h (ebastine-treated group) or 0, 2, and 5 h (terfenadine-treated group) after administration on the first and seventh days. Immediately after sampling, the blood was centrifuged at 3,000 *g* for 10 min at 4°C, and plasma samples were stored at −20°C until analysis. Plasma concentrations of ebastine and carebastine were determined by a high-performance liquid chromatographic (HPLC) method developed at our Developmental Research Laboratories. The detection limits of ebastine and carebastine were 5 ng/mL. Plasma concentrations of terfenadine and its main active metabolite, fexofenadine, were determined by a HPLC method at Shimadzu Techno-Research (Kyoto, Japan). The detection limits of terfenadine and fexofenadine were 10 ng/mL.

### Statistical Analysis

The data represent the mean ± s.e.m. Statistically significant differences from the values in vehicle-treated group were analyzed by parametric Dunnett's test using the SAS system (SAS Institute Inc., Cary, NC). Differences were considered as statistically significant at $P < 0.05$.

## RESULTS

### Effects of Repeated Administration of Ebastine and Terfenadine on ECG in Conscious Dogs

The pretreatment ECG parameters measured were as follows, respectively, in vehicle, terfenadine 30 mg/kg, ebastine 30 mg/kg, and ebastine 100 mg/kg groups: the RR intervals were 693 ± 66, 777 ± 32, 877 ± 44, and 775 ± 65 msec; the QT intervals 221 ± 5, 227 ± 3, 236 ± 5, and 220 ± 8 ms, QTc intervals 216 ± 3, 218 ± 2, 223 ± 4, and 221 ± 6; and the QRS duration was 46 ± 1, 51 ± 4, 55 ± 5, and 46 ± 1 msec. There were no statistically significant differences in the ECG

parameters between the vehicle group and the terfenadine or ebastine group.

On the first day, ebastine at oral doses of 30 and 100 mg/kg did not affect the RR, QT, or QTc intervals in conscious dogs, except that at 30 mg/kg, it slightly shortened the QT intervals compared with the vehicle-treated group at 1 h after administration (Fig. 1). Terfenadine at a single oral dose of 30 mg/kg did not affect the RR, QT, or QTc intervals. Plasma concentration of carebastine reached a peak level of 413 ± 133 ng/mL 2 h after oral administration of ebastine at 100 mg/kg, whereas ebastine was little detected in dog plasma (Fig. 2). Plasma concentration of fexofenadine reached a peak level of 2,204 ± 519 ng/mL 2 h after oral administration of terfenadine at 30 mg/kg, whereas terfenadine was little detected in plasma.

On the seventh day of repeated administrations, ebastine at 30 and 100 mg/kg had a tendency to shorten the RR intervals, whereas it did not affect the QT intervals, leading to a slight, but not significant prolongation of QTc intervals. Terfenadine at oral doses of 30 mg/kg twice a day prolonged the QT and QTc intervals without affecting the RR intervals. Ebastine and terfenadine neither affected the QRS duration nor induced VTs during the experiments. On the seventh day of repeated oral administration of 100 mg/kg ebastine, the plasma concentrations of ebastine and carebastine reached peak levels of 36 ± 18 and 1,939 ± 982 ng/mL, respectively (Fig. 2). The peak plasma concentration of carebastine on the seventh day was higher than that on the first day. On the seventh day of repeated oral administration of 30 mg/kg terfenadine twice a day, the plasma concentrations of terfenadine and fexofenadine reached peak levels of 306 ± 18 and 8,541 ± 1,046 ng/mL, respectively, being higher than those on the first day. However, on the seventh day, the plasma concentrations of terfenadine and fexofenadine before administration of terfenadine (210 ± 28 and 5675 ± 726 ng/mL, respectively) were not markedly higher than those after administration.

In the terfenadine-treated group, no abnormal physical sign such as clonic convulsions, tonic convulsions, salivation, lacrimation, or vomiting was observed, except that 1 out of the 4 dogs induced tremor on the seventh day. In ebastine-treated group, no abnormal physical sign was observed, except that one of the four dogs induced vomiting with administration of ebastine at 100 mg/kg/d on the seventh day.

## Effects of Repeated Administration of Ebastine and Terfenadine on ECG in Conscious Cats

The pretreatment ECG parameters measured were as follows respectively in vehicle, terfenadine 30 mg/kg and ebastine 100 mg/kg groups: the RR intervals were 316 ± 11, 334 ± 41 and 306 ± 18 ms, the QT intervals 173 ± 7, 180 ± 3 and 167 ± 1 ms, QTc intervals 255 ± 9, 262 ± 8 and 249 ± 6, the QRS duration 46 ± 6, 50 ± 6 and 43 ± 8 ms, the JT intervals 127 ± 4, 131 ± 9 and 124 ± 7 ms, and JTc intervals 187 ± 4, 189 ± 7 and 184 ± 8. There were no statistically significant differences in the ECG parameters between vehicle group and terfenadine or ebastine group.

On the first day, ebastine at 100 mg/kg did not affect the ECG parameters in conscious cats (Fig. 3).

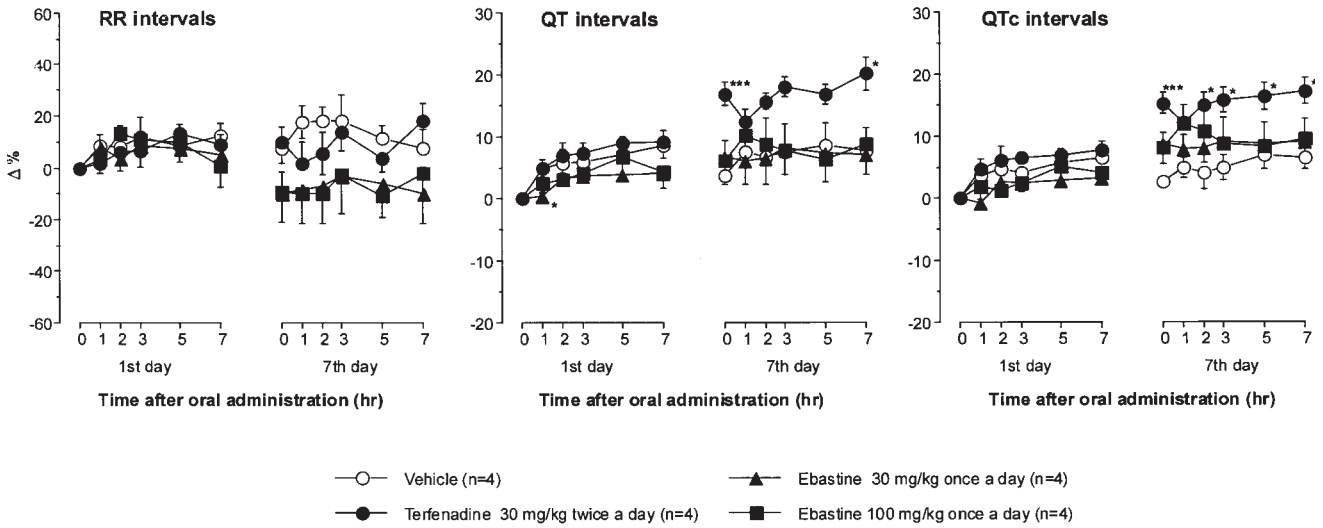


**Fig. 1.** Effects of terfenadine and ebastine on the RR, QT, and QTc intervals in conscious dogs. Terfenadine at 30 mg/kg twice a day was orally administered for 6 days. Ebastine at 30 and 100 mg/kg once a day was orally administered for 6 days. On the seventh day, terfenadine and ebastine were administered only once. Ordinate: the change (%) in the ECG parameters from the values before administrations on the first day. Abscissa: the time (h) after oral administrations on the first and the seventh days. $^{*}P < 0.05$, $^{***}P < 0.001$: compared with the vehicle-treated group at same time point.

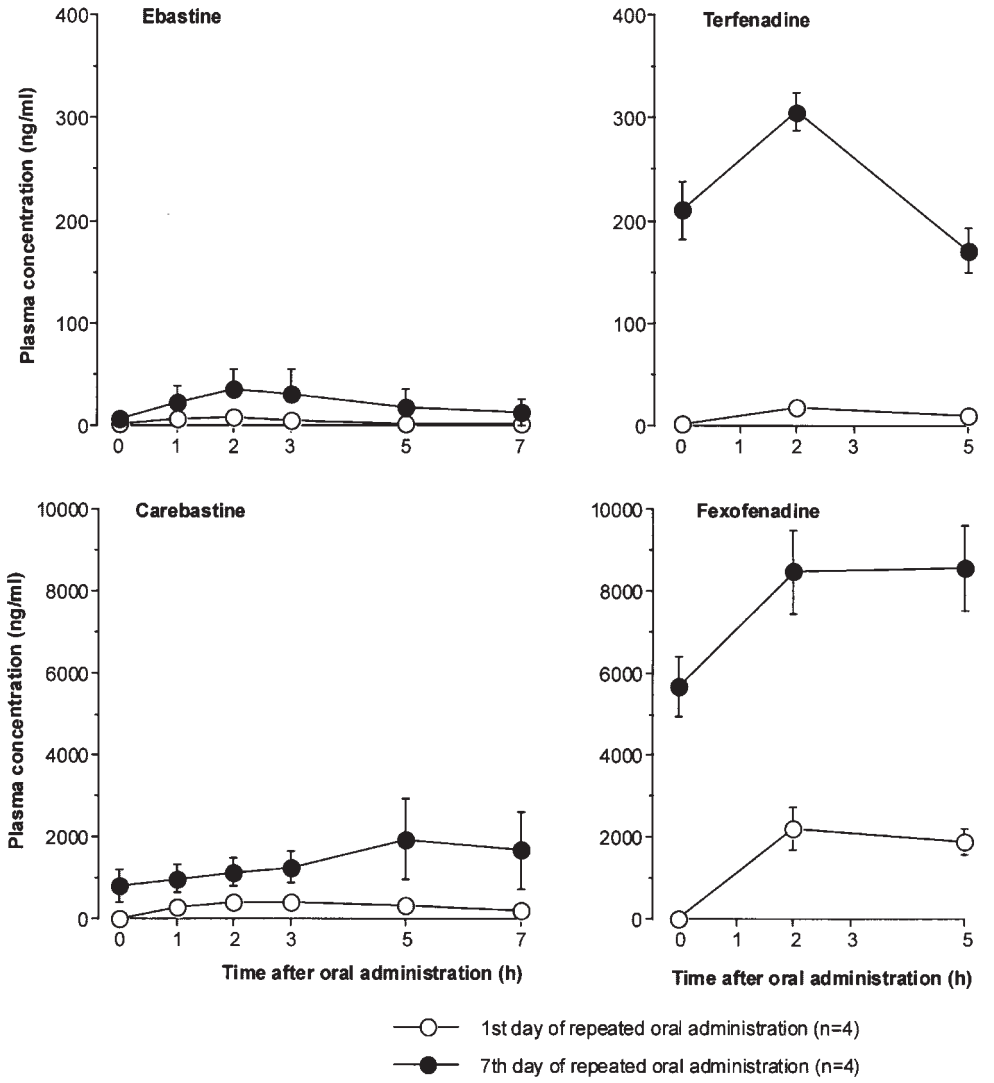


**Fig. 2.** Plasma concentrations of ebastine, terfenadine, and their active metabolites on the first and seventh days of repeated oral administrations in conscious dogs. **Left:** Plasma concentrations of ebastine (upper) and its active metabolite, carebastine (lower), after repeated oral administrations of 100 mg/kg once a day. The detection limits of ebastine and carebastine were 5 ng/mL. **Right:** Plasma concentrations of terfenadine (upper) and its active metabolite, fexofenadine (lower), after repeated oral administrations of terfenadine at 30 mg/kg twice a day. The detection limits of terfenadine and fexofenadine were 10 ng/mL.

On the other hand, terfenadine at a single oral dose of 30 mg/kg slightly prolonged QTc ($P = 0.05119$) and JTc intervals ($P < 0.05$) without significantly affecting the other parameters.

On the seventh day of repeated administrations, ebastine at oral doses of 100 mg/kg once a day was without effects on the ECG parameters. On the other hand, terfenadine at oral doses of 30 mg/kg twice a day markedly prolonged the QT and QTc intervals, QRS duration, and JT and JTc intervals. Furthermore, as shown in Fig. 4, terfenadine induced VTs on the sixth day after repeated administration in one of four cats and ventricular premature beats before administration of terfenadine on the seventh day in another cat. In the ebastine-treated group, no abnormal physical sign such as convulsions, salivation, lacrimation, or vomiting was not observed, except for a significant ($P < 0.05$) weight loss of $0.48 \pm 0.11$ kg as compared with the vehicle-treated group ($0.03 \pm 0.03$ kg).

## DISCUSSION

In the present study, terfenadine was found to prolong the QT and QTc intervals by 20% of each pretreatment value on the seventh day of the repeated oral administration in conscious dogs,

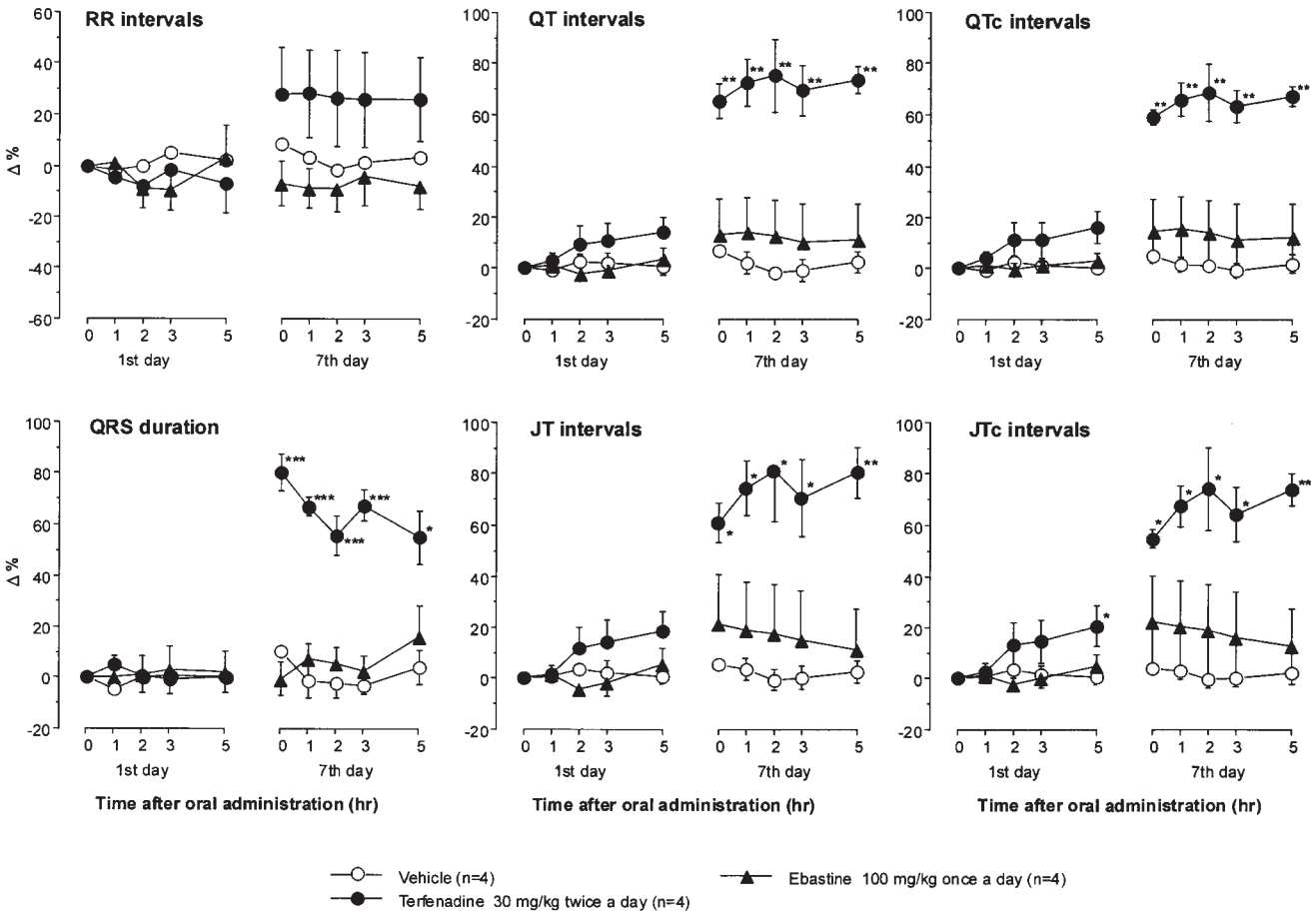


**Fig. 3.** Effects of terfenadine and ebastine on the ECG in conscious cats. Terfenadine at 30 mg/kg twice a day was orally administered for 6 days. Ebastine at 100 mg/kg once a day was orally administered for 6 days. On the seventh day, terfenadine and ebastine were administered only once. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$: compared with the vehicle-treated group at same time point.

although it did not affect the QT or QTc intervals on the first day. However, terfenadine did not induce VTs or TdP. Similar results were reported in anesthetized dogs, i.e., that terfenadine prolonged the QT and QTc intervals without inducing VTs [Usui et al., 1998]. The reason why terfenadine did not induce VTs in dogs may be explained by the previous findings, namely, 1) several drugs with proarrhythmic potential induced TdP only in dogs with severely disturbed cardiac functions, e.g., chronic bradycardia caused by atrioventricular (AV) block [Hammond et al., 2001; Weissenburger et al., 2000; Eckardt et al., 1998], and 2) ibutilide, a class III antiarrhythmic agent, induced TdP in dogs with chronic AV block but not with acute AV block [Chen et al., 1999]. Therefore, it may be difficult for drugs to induce VTs and TdP in intact dogs.

On the seventh day, the mean plasma concentrations of terfenadine and fexofenadine reached 306 ng/mL (0.65 μM) and 8,541 ng/mL (17.0 μM), respectively, being much higher than those on the first day. At similar concentrations on the seventh day, terfenadine, but not fexofenadine, has been shown to inhibit $I_{kr}$ in isolated ventricular myocytes [Ducic et al., 1997; Woosley, 1996]. In addition, the peak plasma concentrations of fexofenadine in dogs on the seventh day were about 30 times higher than the maximum plasma concentration ($C_{max}$; 236–245 ng/mL) at the therapeutic doses of terfenadine in humans [Honig et al., 1992; Awni et al., 1997]. These results indicate that, when repeatedly overdosed with terfenadine, the increases in plasma concentration of terfenadine lead to prolongation of QT and QTc intervals in conscious dogs. On the seventh day, plasma concentration of terfenadine and fexofenadine before administration of terfenadine did not appear to be much lower than that after administration suggesting possibility of a metabolic saturation of terfenadine.

In conscious cats, terfenadine markedly prolonged the QT and QTc intervals by 60–80% of each pretreatment value by repeated administration. Furthermore, the drug prolonged the QRS duration

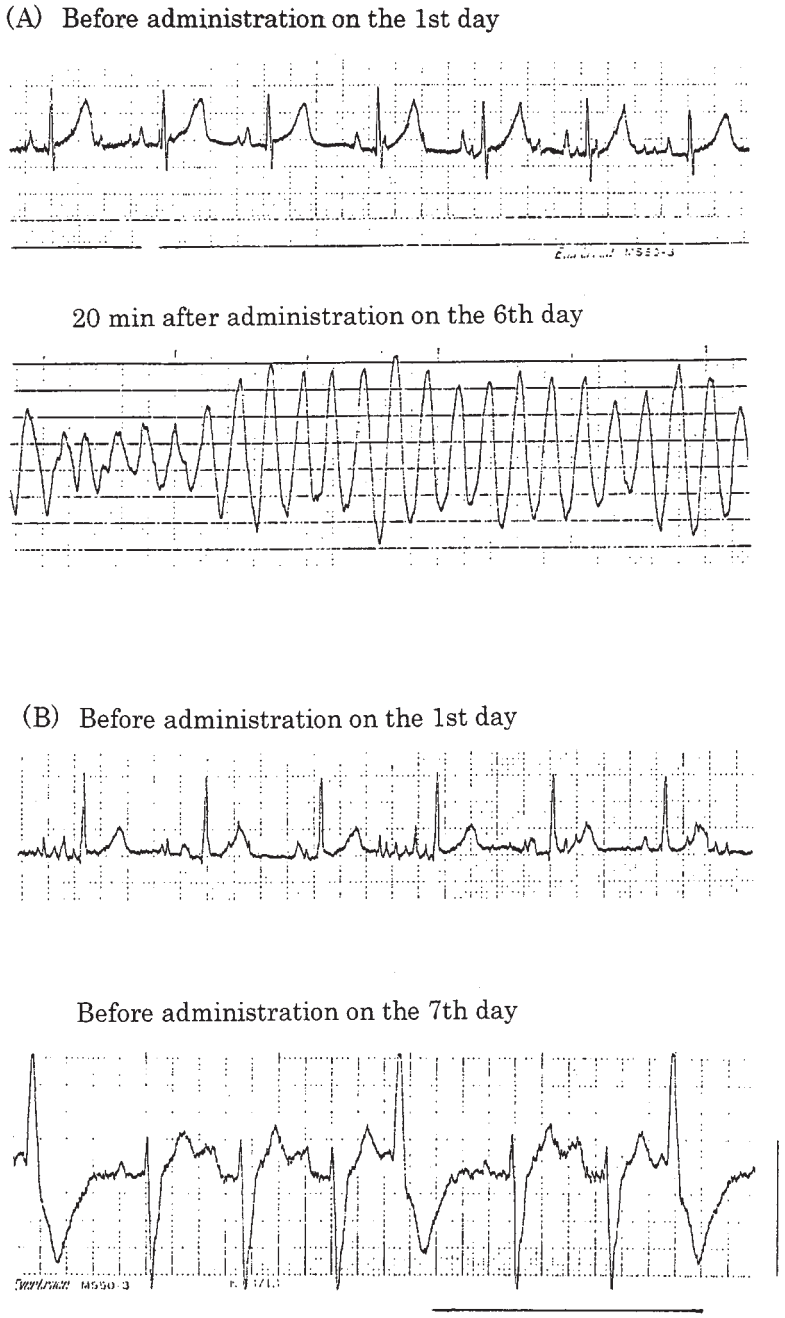


**Fig. 4.** Terfenadine-induced ventricular tachyarrhythmia (A) and ventricular premature beats (B) in cats. **(A)** Upper: Before administration of terfenadine at the first day; Lower: 20min after oral administration of terfenadine on the sixth day. **(B)** Upper: Before administration of terfenadine on the first day; Lower: before administration of terfenadine on the seventh day. Vertical and horizontal bars represent 1 mV and 1 sec, respectively.

and JT and JTc intervals, and induced VTs and ventricular premature beats. This is the first report showing that terfenadine prolonged QRS duration and induced TdP-like phenomenon in conscious cats. It is well known that the potent inhibition of $I_{kr}$ often leads to the prolongation of ventricular repolarization and that excess prolongation of ventricular repolarization often induces VTs. In addition, it has been reported that terfenadine inhibits $I_{kr}$ in cat isolated ventricular myocytes and prolongs QT intervals in isolated cat hearts [Woosley, 1996]. Therefore, the terfenadine-induced changes in the ECG parameters may be mediated, at least partly, through its inhibition of $I_{kr}$. However, at the same doses, terfenadine did not

prolong the QRS duration or induce VTs in conscious dogs. In addition, the prolongations of QT and QTc intervals in conscious cats were more potent than in conscious dogs. At the present time, it is unclear why terfenadine showed proarrhythmic effect more readily in cats than in dogs. Recently, we demonstrated that cisapride, a gastroprokinetic drug with proarrhythmic effect [De Ponti et al., 2000; Wiseman and Faulds, 1994], prolonged the QT and QTc intervals and QRS duration in conscious cats [Kii et al., 2001]. Accordingly, these results suggest that a conscious cat is a suitable animal for evaluating the proarrhythmic potential of drugs, although additional studies on the relationship between plasma concentration of drugs and the proarrhythmic potential in cats are needed.

Repeated administration of ebastine had no significant effect on the QT and QTc intervals in conscious dogs. On the seventh day of repeated oral administration of 100 mg/kg ebastine, the plasma concentrations of ebastine and carebastine reached peak levels of 36 ng/mL and 1,939 ng/mL, respectively. These results were consistent with the previous evidence that ebastine and carebastine were without effect on the action potential duration in isolated guinea pig papillary muscles [Kii et al., 1996] and isolated rabbit Purkinje fibers [Cavero et al., 1999], and that ebastine at intravenous doses of 0.1–3 mg/kg does not either affect the RT intervals in ECG in anesthetized dogs [Nakamura et al., 1998] or the QTc intervals in anesthetized guinea pigs [Llenas et al., 1999]. In addition, the peak plasma concentrations of carebastine on the seventh day in dogs are about 20 times $C_{max}$ (115 ng/mL) at therapeutic doses of ebastine in humans [Yamaguchi et al., 1994]. On the other hand, ebastine has been shown to inhibit $I_{kr}$ in guinea pig isolated ventricular myocytes [Ko et al., 1997] and prolong QTc intervals in anesthetized guinea pigs at the high intravenous doses of 10–50 mg/kg [Hey et al., 1996]. However, the concentrations of ebastine inhibiting $I_{kr}$ were about 235 times higher than the plasma ones observed in patients receiving clinically acceptable ebastine dosage of 20 mg/d for 7 days [Ten Elick et al., 2001]. Furthermore, from the previous report [Nakamura et al., 1998], the plasma concentrations of ebastine in anesthetized guinea pigs at intravenous doses of 10–50 mg/kg were predicted to be 500–2,500 times higher than the clinical ones. Ebastine slightly shortened the RR intervals in conscious dogs, and it is well known that TdP is associated with bradycardia (lengthening of the RR intervals). Accordingly, ebastine shows no proarrhythmic effect in these models, supporting the result of the high-dose clinical study described by Malik [2001] demonstrating the absence of ebastine-induced QTc intervals prolongation, when appropriately corrected for changes in heart rate.

In safety pharmacology, anesthetized animals have been used to evaluate the proarrhythmic potential of drugs. However, it has been reported that several anesthetics prolong the QT and/or QTc intervals [Hammond et al., 2001], and that the apparent proarrhythmic potential of drugs differs according to the anesthetic agents used [Weissenburger et al., 2000; Yamamoto et al., 2001]. Furthermore, in anesthetized animals, the drugs are generally administered intravenously, whereas most noncardiac drugs with proarrhythmic potential are administered orally in humans. The present study demonstrated that repeated oral administration of terfenadine prolonged the QT and QTc intervals in conscious dogs and cats and induced VTs and ventricular premature beats in cats. Therefore, it may be a useful model to evaluate proarrhythmic potential of drugs in conscious animals using repeated administration by the clinical route, although additional studies using other drugs are necessary.

In conclusion, the present results indicate that the proarrhythmic potential of terfenadine can be evaluated in conscious dogs, and especially in conscious cats, by repeated administration by the clinical route, and that ebastine shows no proarrhythmic effect in these models.

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