J. Pharm. Pharmacol. 1997, 49: 458–462
Received November 6, 1996
Accepted December 5, 1996

A Comparative Pharmacokinetic–Pharmacodynamic Study of the Electrocardiographic Effects of Epinastine and Terfenadine in Rats

HISAKAZU OHTANI, HAJIME KOTAKI, YASUFUMI SAWADA* AND TATSUJI IGA

*Department of Pharmacy, The University of Tokyo Hospital, Faculty of Medicine, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113 and *Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812, Japan*

Abstract

The effects of epinastine hydrochloride and terfenadine on electrocardiographic (ECG) parameters in rats were investigated from a pharmacokinetic and pharmacodynamic perspective.

Epinastine hydrochloride (1 or 3 mg kg^{-1} h^{-1}) or terfenadine (5, 10 or 15 mg kg^{-1} h^{-1}) was intravenously infused into rats anaesthetized with urethane and α-chloralose. The changes in the QT interval derived from limb lead II and the chest lead, heart rate and PR interval were analysed. The time-course of the plasma drug-concentration of each drug was also investigated. Terfenadine prolonged the QT interval in an infusion-rate-dependent manner; its EC50 value was 792–1039 ng mL^{-1}. An obvious QT prolongation was, moreover, observed even at a plasma terfenadine concentration of 100–200 ng mL^{-1}, which is clinically quite high, but might be achieved under a definite condition such as a restrained terfenadine metabolism. Terfenadine also induced PR prolongation and bradycardia in an infusion-rate dependent manner. Epinastine slightly increased the heart rate, but did not affect any of the other ECG parameters even at a plasma concentration of 400 ng mL^{-1}, which is more than 10 times the maximum concentration attained after an ordinary dosage regimen in man.

We conclude that epinastine might have an advantage over terfenadine in avoiding adverse electrocardiographic reactions.

Terfenadine is widely used as a non-sedating antihistamine. Clinically, however, cases of cardiac arrhythmia (torsades de pointes) induced by terfenadine have been reported (Davies et al 1989; Monahan et al 1990; McConnell & Stanners 1991). When administered orally, terfenadine is almost completely converted by hepatic first-pass metabolism to the active metabolite terfenadine carboxylate which does not evoke an ECG disturbance (Garteiz et al 1982; Woosley et al 1993). Elevation of unchanged terfenadine concentration in plasma, which leads to cardiac arrhythmia, can, however, occur after an overdose or under the concomitant use of metabolic inhibitors (Davies et al 1989; Monahan et al 1990).

Recently, another non-sedating antihistamine, epinastine hydrochloride, became clinically available. Although, because epinastine is eliminated mainly by renal excretion (Boehringer Ingelheim 1994), it is not considered to be susceptible to metabolic inhibitors, its direct effect on ECG has not been thoroughly investigated.

We have already investigated the ECG effects of quinidine and terfenadine from the viewpoint of pharmacokinetics and pharmacodynamics in anaesthetized rats; the results were in good agreement with the clinically observed ECG disturbance, that is, QT-prolongation (Ohtani et al 1996a).

We now report a study of the ECG effects of epinastine and terfenadine in anaesthetized rats from the viewpoint of pharm-acokinetics and pharmacodynamics, while avoiding adverse ECG effects caused by these agents.

Correspondence: H. Ohtani, Department of Pharmacy, The University of Tokyo Hospital, Faculty of Medicine, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan.

Materials and Methods

Chemicals

Terfenadine and epinastine hydrochloride were kind gifts from Marion Merrell Dow K. K. (Osaka, Japan) and Nippon Boehringer Ingelheim (Kawanishi, Japan), respectively. All other chemicals used were of reagent grade.

Pharmacodynamic experiments

Male Sprague–Dawley rats, 300–450 g, were purchased from Nippon Seibutsu Zairyou Center and anaesthetized with a combination of urethane and α-chloralose (1·2 mg kg^{-1} and 30 mg kg^{-1} i.p., respectively). The precordial and limb hair was removed by use of hair-removing cream (Kanebo, Tokyo). With the animals restrained in a supine position, the trachea, right jugular vein and right carotid artery were cannulated with polyethylene tubing. The body temperature was maintained at 37·5 ± 0·5°C throughout the experiments by means of a hot-water-circulating heat pad placed beneath the animals. The electrocardiograph (ECG) was recorded and analysed by the method of Ohtani et al (1996a). The QT interval was defined as the time from the start of the QRS complex to the end of the T wave, at which the amplitude of the T wave declines to 10% of its maximum. QT(II), defined as the QT interval from the limb lead II, and QT(V), the precordial chest lead, were simultaneously analysed.

After stabilization of the ECG and of body temperature, a physiological salt solution (NaCl, 135 mM; $NaHCO_3$, 11·9 mM; KCl, 5·4 mM; $CaCl_2$, 1·8 mM; $MgCl_2$, 1·0 mM) was infused into the jugular vein at a rate of 2·32 mL h^{-1} for 10 min by means of an infusion pump (Model 975, Harvard

Apparatus, USA). Epinastine hydrochloride (1 or 3 mg kg^{-1} h^{-1}) or terfenadine (5, 10 or 15 mg kg^{-1} h^{-1}) was then infused. Epinastine and terfenadine were dissolved in the physiological salt solution, with terfenadine dissolved according to the method previously described by Webb (1976); briefly, terfenadine was dissolved in a stoichiometrically equivalent amount of oleic acid and benzyl alcohol, and subsequently dissolved in the physiological salt solution by use of surfactant (Tween 80; polysorbate 80 USP XIX).

ECG recordings were performed before the administration of the physiological salt solution, from 1 min before to 19 min after the start of infusion and at 20, 30, 40, 50 and 60 min post-infusion.

Pharmacokinetic experiments

Pharmacokinetic studies were performed with different animals from those used for the pharmacodynamic experiments. All conditions were identical with those described above for the pharmacodynamic experiments, with the exception that after drug administration blood samples (250 μL) were collected from the carotid artery at 1, 3, 5, 15, 30, 45 and 60 min for epinastine and at 2, 5, 10, 20, 30 and 60 min for terfenadine. Blood samples were centrifuged to furnish plasma (100 μL). The drug concentrations in the plasma were determined by the HPLC-UV procedures previously described (epinastine, Ohtani et al 1996b; terfenadine, Ohtani et al 1996a).

Model analysis and statistics

Pharmacokinetic parameters such as the half-life of the elimination phase ($t_{\frac{1}{2}\beta}$), distribution volume at steady state (Vd_{SS}) and total clearance (CL) were calculated by fitting the time profiles of plasma concentration at all infusion rates to the 2-compartment model, using the non-linear least-squares method. For terfenadine at a high infusion rate (15 mg kg^{-1} h^{-1}), the plasma concentration datum at 60 min was excluded because the sinus rhythm was not preserved in some animals. The effect compartment model by Sheiner et al (1979) was used for the analysis of QT prolongation with terfenadine because a delay in the effects against the plasma concentration was observed. The plasma concentration (C_p) at each time, used here as the input function, was the value estimated by linear interpolation of the concentration profile determined in pharmacokinetic experiments. The pharmacological effect (E) was assumed to be related to the concentration in the effect-compartment (C_e) by equation 1:

$$E = E_{max} \cdot C_e/(EC50 + C_e) \quad (1)$$

where E_{max} and EC50 indicate the maximum effect and concentration where the half-maximum effect was evoked, respectively. Differentiation of equation 1 gives equation 2:

$$dE/dt = [E_{max} \cdot EC50/(EC50 + C_e)^2]dC_e/dt \quad (2)$$

Combining equations 2 and 3 gives equation 4:

$$dC_e/dt = k_{e0} \cdot (C_p - C_e) \quad (3)$$

$$dE/dt = k_{e0} \cdot (E_{max} - E) \times [(C_p \cdot E_{max} - C_p \cdot E - E \cdot EC50)/E_{max} \cdot EC50] \quad (4)$$

where k_{e0} indicates the rate constant for elimination from the effect compartment. The pharmacodynamic parameters, E_{max}, EC50 and k_{e0} were derived by simultaneous fitting of the ECG effects (E) at all infusion rates to equation 4 using the non-linear least-squares method.

Results

Relationship between basal QT interval and heart rate

Fig. 1 shows the relationship between QT interval (lead II) and heart rate before the administration of drugs. Analysis of ECG parameters obtained from 32 rats did not result in any indication of correlation between QT interval and heart rate ($r^2 = 0.007$).

Effects of epinastine on rat ECG

Fig. 2 shows the time profiles of changes in the ECG parameters QT-II interval, QT-V interval, PR interval and heart rate, during constant intravenous infusion of epinastine into rats. The intravenous infusion of epinastine, even at a higher infusion rate, did not have any effect on the QT or PR intervals. Although a slight increase in heart rate was observed, no apparent dose-dependency was observed.

Effects of terfenadine on rat ECG

Fig. 3 shows the time profiles of changes in the ECG parameters QT-II interval, QT-V interval, PR interval and heart rate, during constant intravenous infusion of terfenadine into rats. Terfenadine prolonged the QT and PR intervals in an infusion-rate-dependent manner whereas injection of vehicle did not affect the ECG parameters. The sinus rhythm was lost in some animals after 50 or 60 min at a infusion rate of 15 mg kg^{-1} h^{-1}, so ECG parameters at these times were not indicated. Table 1 shows the pharmacodynamic parameters derived from the analysis using the effect-compartment model. The EC50 values of terfenadine-induced QT prolongation on lead II and the chest lead were 1·039 and 0·792 μg mL^{-1}, respectively. The E_{max} value from each lead was essentially identical at around 30 ms.

Pharmacokinetic profile of epinastine

Fig. 4 shows the time profiles of the plasma–concentration of epinastine during constant intravenous infusion of epinastine

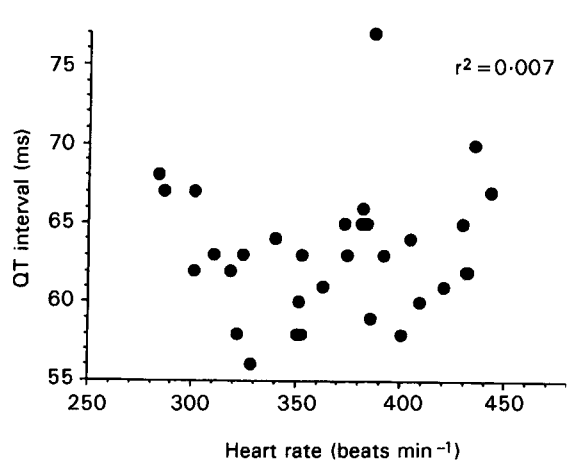

FIG. 1. Relationship between heart rate and QT interval before administration of terfenadine.

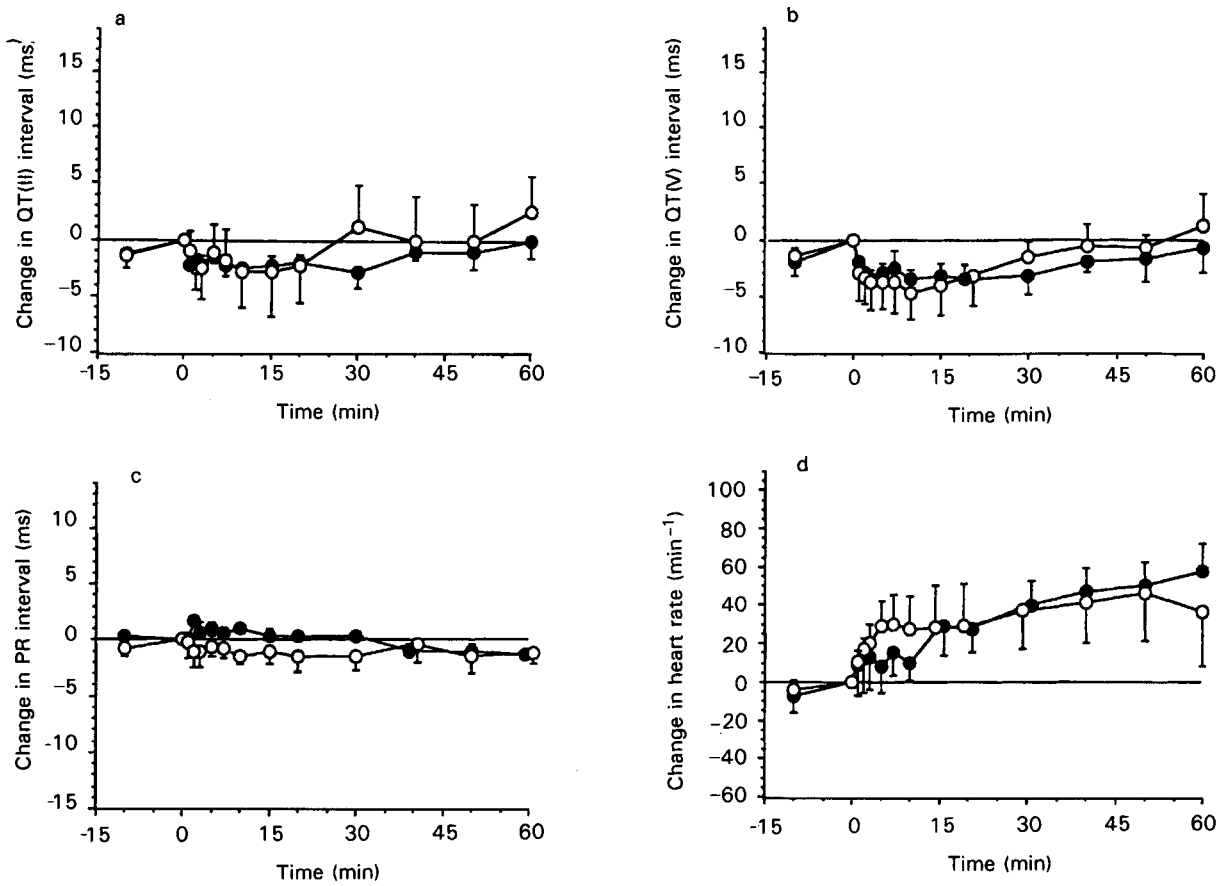

FIG. 2. Time-courses of electrocardiographic effects resulting from the constant intravenous infusion of epinastine hydrochloride. a. Change in QT interval from lead II, b. change in QT interval from the chest lead, c. change in PR interval, d. change in heart rate. ● 1 mg kg^{-1} h^{-1}, ○ 3 mg kg^{-1} h^{-1} (n = 4–5; mean ± s.e.m.).

hydrochloride at rates of 1 or 3 mg kg^{-1} h^{-1}. The plasma-concentration profiles nearly became stable at 60 min at all infusion rates. Linear kinetics were observed within the range investigated here. The pharmacokinetic parameters of epinastine are listed in Table 2. The concentration range in this study was more than 10 times the clinical range (10–30 ng mL^{-1}; Boehringer Ingelheim 1994; indicated as the hatched area in Fig. 4).

Pharmacokinetic profile of terfenadine

Fig. 5 shows the time profiles of the plasma-terfenadine concentration during constant intravenous infusion of terfenadine at a rate of 5, 10 or 15 mg kg^{-1} h^{-1}. Although linear kinetics were observed at infusion rates of 5 or 10 mg kg^{-1} h^{-1}, a distinctly non-linear profile was observed, especially at 60 min, at an infusion rate of 15 mg kg^{-1} h^{-1}. The pharmacokinetic parameters, calculated from all data except for the point at 60 min at a rate of 15 mg kg^{-1} h^{-1}, are indicated in Table 2.

Discussion

Many cases of QT prolongation followed by severe arrhythmia (torsades de pointes) have been reported with the use of terfenadine (Davies et al 1989; Monahan et al 1990; McConnell & Stanners 1991). Even though unmetabolized terfenadine potently inhibits cardiac potassium channels (Rampe et al 1993; Woosley et al 1993), orally-administered terfenadine is ordinarily completely metabolized to its active metabolite which is electrocardiographically inactive (Garteiz et al 1982; Rampe et al 1993; Woosley et al 1993). Cardiac arrhythmia can develop when unchanged terfenadine appears in plasma as a result of overdose or inhibition of first-pass metabolism (Davies et al 1989; Monahan et al 1990).

No cases of QT prolongation or torsades de pointes have been reported for epinastine. Epinastine essentially does not undergo first-pass metabolism and thus unchanged epinastine ordinarily appears in the plasma. Because this drug is, moreover, mainly eliminated by renal excretion (Boehringer Ingelheim 1994), the arrhythmogenic risk of epinastine might be lower than that of terfenadine. No quantitative analysis of the direct ECG effects of epinastine has, however, been performed.

To evaluate the safety of epinastine and the possible substitution of terfenadine by epinastine, it is essential to investigate the direct ECG effects of epinastine and compare them with those of terfenadine from a pharmacokinetic and pharmacodynamic viewpoint. The analysis of ECG parameters using rats provides quantitative information for assessment of drug-induced QT prolongation (Ohtani et al 1996a). Because QT prolongation is employed as a clinical index for predicting torsades de pointes (Faber et al 1994), we examined the effects of terfenadine and epinastine on the QT interval of rat ECGs as

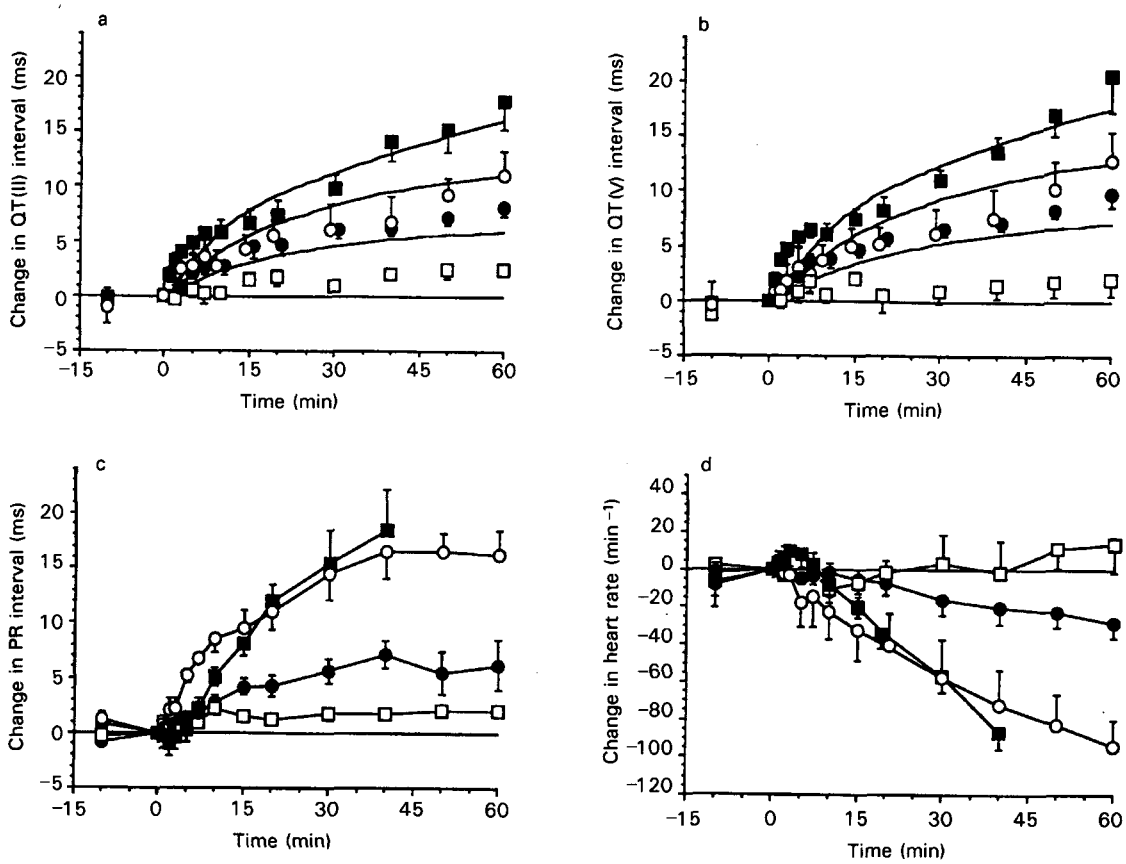

FIG. 3. Time-courses of electrocardiographic effects resulting from the constant intravenous infusion of terfenadine. a. Change in QT interval from lead II, b. change in QT interval from the chest lead, c. change in PR interval, d. change in heart rate. □ Control (vehicle), ● 5 mg kg^{-1} h^{-1}, ○ 10 mg kg^{-1} h^{-1}, ■ 15 mg kg^{-1} h^{-1} (n = 4–7; mean ± s.e.m.).

Table 1. Pharmacodynamic parameters for terfenadine-induced QT prolongation.

Parameter	Lead II	Chest lead
Rate constant for elimination from the effect compartment (min^{-1})	0·0604 ± 0·0206	0·0472 ± 0·0196
Maximum effect (ms)	30·3 ± 7·09	30·4 ± 6·77
Concentration for half-maximum effect (μg mL^{-1})	1·039 ± 0·468	0·792 ± 0·400

Values are means ± s.d.

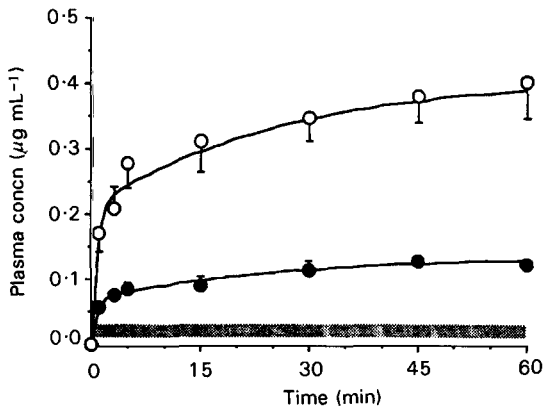

FIG. 4. The pharmacokinetic profiles of epinastine hydrochloride during constant intravenous infusion to rats; the clinical concentration is indicated as the hatched range. ● 1 mg kg^{-1} h^{-1}, ○ 3 mg kg^{-1} h^{-1} (n = 4; mean ± s.e.m.).

an index of arrhythmogenicity. Although the corrected QT interval (QTc) derived from 'Bazett's formula' (Bazett 1920) has been widely used clinically, the QTc is based upon the ECG from man and it is, therefore, questionable whether this correction can be applied directly. In fact, contrary to the findings of Bazett, we failed to demonstrate the relationship between basal QT interval and heart rate in rats ($r^2 = 0·007$; Fig. 1). The actual QT interval, rather than QTc might, moreover, be preferable for indicating torsades de pointes (Keren et al 1981). We therefore employed the actual QT interval without correction as an index of arrhythmogenicity, even though the influence of bradycardia might not be excluded completely.

At the lowest rate of terfenadine, 5 mg kg^{-1} h^{-1}, an apparent QT prolongation was also provoked in this study. These results are essentially identical to data reported previously (Ohtani et al 1996a). At the infusion rate given above,

Table 2. Pharmacokinetic parameters of epinastine and terfenadine.

Parameter	Epinastine	Terfenadine
Half-life of the elimination phase (min)	19·1	27·1
Distribution volume at steady state (mL kg^{-1})	1670	4750
Total clearance (mL min^{-1} kg^{-1})	121	254

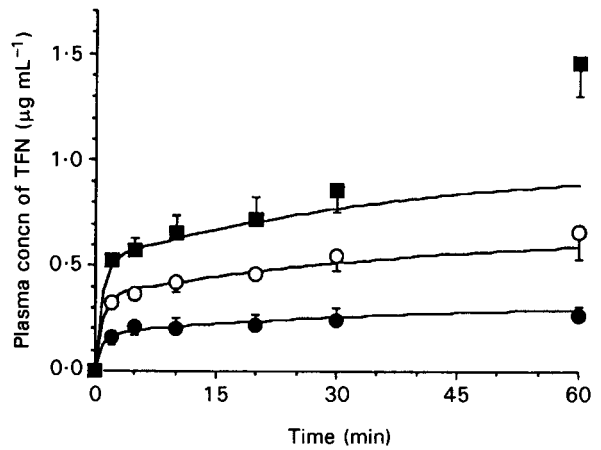

FIG. 5. The pharmacokinetic profiles of terfenadine during constant intravenous infusion into rats. ● 5 mg kg^{-1} h^{-1}, ○ 10 mg kg^{-1} h^{-1}, ■ 15 mg kg^{-1} h^{-1} (n = 3–4; mean ± s.e.m).

the plasma concentration of terfenadine was 100–200 ng mL^{-1}, which is significantly higher than the clinical concentration of terfenadine after an ordinary dosage regimen (< 5 ng mL^{-1}). Terfenadine, however, acts clinically as a prodrug and terfenadine undergoes extensive first-pass metabolism. Because the bioavailability of unchanged terfenadine is greatly elevated under conditions such as overdose or restrained hepatic metabolism, the plasma concentration of terfenadine is highly susceptible. In fact, unchanged terfenadine has been detected at high concentrations (43–57 ng mL^{-1}) in plasma samples collected upon hospital admission after seizures (Davies et al 1989; Monahan et al 1990; McConnell & Stanners 1991). The actual concentration during the event might be higher and comparable with the concentrations observed in this study.

The kinetics of epinastine are less susceptible than those of terfenadine, because epinastine undergoes virtually no first-pass metabolism and is mainly eliminated by renal excretion (Boehringer Ingelheim 1994). Here, high concentrations (10 times higher than the clinical range) of epinastine did not affect the QT interval. Judging from these results, epinastine might have an advantage over terfenadine in avoiding adverse ECG effects. Although epinastine slightly increased the heart rate, this observation accords with studies reported in dogs (Ohara et al 1992).

For epinastine, the conventional 2-compartment model was applicable for explanation of the kinetics. Although the calculated clearance exceeds the renal blood flow, this might be because of the lack of sampling points at the terminal phase; the half-life of the elimination phase is, indeed, reported to be over 120 min (Ohtani et al 1996b).

The kinetics of terfenadine were linear against infusion rate at 5 or 10 mg kg^{-1} h^{-1}, although apparent non-linearity developed after 30 min at an infusion rate of 15 mg kg^{-1} h^{-1} (Fig. 5). This decrease in clearance might result from the decrease in hepatic blood flow as a result of bradycardia. In addition, the calculated clearance for terfenadine exceeds the hepatic blood flow for the identical reason as for epinastine.

In conclusion, in contrast with terfenadine-induced QT prolongation at concentrations possibly achieved under certain conditions such as restrained metabolism, epinastine did not evoke a QT prolongation at high concentrations, even at 10 times the clinical range. Epinastine might, therefore, have an advantage over terfenadine in the avoidance of adverse ECG reaction.

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