INTRODUCTION

Several drugs have been withdrawn from the market recently due to cardiovascular side effects associated with a ventricular tachyarrhythmia known as Torsades de Pointes (TdP) (Redfern et al., 2003). Because most drugs that induce TdP in man prolong the QT interval (Redfern et al., 2003), greater emphasis is placed on identifying QT prolongation risk of new chemical entities in early stage development. In that early stage, in vitro tests for screening QT risk, such as human ether-a-go-go-related gene (hERG) and action potential duration (APD) assays, are performed mainly because of the limited amount of test substance required (Guth et al., 2004). However, in vitro tests do not take into account such effects as the potential impact of plasma protein binding, formation of active metabolites, or additional cardiac hemodynamics, and the results may be inconsistent with clinical QT outcomes. The predictability of in vivo tests using telemetered dogs or monkeys for the clinical QT liability of drugs has been validated (Toyoshima et al., 2005; Ando et al., 2005; Hanson et al., 2006) but a considerably larger amount of test substance is needed than with in vitro testing. Recently, common marmosets have been in the limelight as experimental animals in the early development stage because of their small size and thus small amount of test drug. In conclusion, telemetry studies in common marmosets are useful for predicting clinical QT prolonging potential of drugs in early stage development and require only a small amount of test drug.
study focused on the utility of the animal for the entire cardiovascular system and not specifically the predictability of drug-induced QT interval prolongation.

When examining the effect of a drug on QT interval, it is necessary to correct the QT intervals against RR intervals using QT/RR correction formulas because the QT interval adapts to changes in the RR interval (or heart rate). General correction formulas from Bazett (Bazett, 1920) and Fridericia (Fridericia, 1920) have been used to evaluate the QT liability of drugs in dogs and monkeys (Toyoshima et al., 2005; Ando et al., 2005; Hanson et al., 2006), however, an individual rate correction was recently proposed to be more appropriate (Miyazaki and Tagawa, 2006); however, there has been no information available on this individual QT/RR correction method used with common marmosets.

The purpose of this study was twofold. (1) To determine the QT correction method suitable for use with common marmosets from among the two generally used formulas and the individual rate correction. (2) To demonstrate the accuracy of prediction of the QT liability of drugs by comparing the effects on QT interval of clinical and in vitro hERG inhibitions.

MATERIALS AND METHODS

Animals

Common marmosets obtained from Clea Japan, Inc. (Tokyo, Japan) were used in this study. The animals were handled according to the protocol approved by the Ethical Committee for Animal Welfare of Chugai Pharmaceutical Co., Ltd. The animals received solid food once daily and water ad libitum, and were individually housed in stainless steel cages (W: 465 mm, D: 465 mm, H: 565 mm) in environmentally controlled, HEPA-filtered rooms with 12 hr of light (7:00-19:00), a temperature range of 28 ± 2°C, and a relative humidity range of 55 ± 15%.

Drugs

Two compounds known to cause QT interval prolongation in humans, the histamine H₁ blocker astemizole and the anti-arrhythmic drug dl-sotalol hydrochloride (dl-sotalol), and two compounds known to not cause QT interval prolongation in humans, the adrenergic β receptor antagonist dl-propranolol hydrochloride (dl-propranolol) and the calcium channel blocker nifedipine, were selected for this study (Omata et al., 2005). All compounds were purchased from Sigma Chemical Co. (St. Louis, MO, USA). dl-Sotalol and dl-propranolol were dissolved in distilled water (DW). Nifedipine or astemizole was formulated as a suspension in 0.5% carboxyl-methylcellulose sodium (CMC) (Wako Pure Chemical Industries, Ltd., Osaka, Japan) in DW with or without 1.5% dimethyl sulfoxide (DMSO) (Wako Pure Chemical Industries, Ltd.).

Animal preparation

Four common marmosets (250-400 g, 2 males and 2 females) were surgically instrumented with telemetry transmitters (TL11M2-C50-PXT, Data Sciences International, Arden Hills, MN, USA). After intramuscular injections of ketamine hydrochloride at 50 to 70 mg/kg and xylazine hydrochloride at 5 to 7 mg/kg, the anesthetized animals were instrumented subcutaneously with leads of a limb lead II electrocardiogram (ECG). The positive lead was positioned between the left 7th and 8th ribs while the negative lead was positioned on the first sternum. The telemetered animals were given 25 mg/head streptomycin intramuscularly post surgery and were allowed to recover for at least 1 month.

ECG recording

ECG was transmitted to the telemetry transmitter at a time constant of 2 sec. The transmitted ECG data was recorded by a data acquisition system (ART, Data Sciences International) at 1 kHz and analyzed using data analysis software (HEM ver 4.1, NOTOCORD Systems SAS, Croissy sur Seine, France). The ECG measurement was performed under quiet conditions in an animal room remote from the data acquisition, analysis and storage room. Entry to the animal room was restricted except for physical checks, dosing, feeding the animals and cleanup of room and cages.

Cardiovascular ECG

First, we conducted a comparative evaluation of three QT/RR correction methods. ECGs were recorded continuously for 24 hr, and QT and RR intervals were measured every 6 min over 24 hr with 10 consecutive ECG waves analyzed at each point. The QT interval was then corrected against the RR interval by generic formulas proposed by Bazett (1920) and Fridericia (1920) and the individual rate correction derived from the method initially described by Spence et al. (1998) and subsequently modified by Miyazaki and Tagawa (2002). The corrected QT (QTC) intervals were re-expressed to the reference cycle length (RRref = 400 ms) in order to compare the efficiencies of the methods. The reference cycle length was determined using the average common marmoset heart rate of 150 beats/min (bpm). The modified generic formulas used in this study were:
The individual rate-corrected QT (QTci) intervals were obtained according to the following expressions:

\[
\text{QTcB} = \text{RR}_{1/2}^{1/2} \times \frac{\text{QT}}{\text{RR}^{1/2}} \quad \text{(modified Bazett)}
\]

\[
\text{QTcF} = \text{RR}_{1/3}^{1/3} \times \frac{\text{QT}}{\text{RR}^{1/3}} \quad \text{(modified Fridericia)}
\]

The individual rate-corrected QT (QTci) intervals were obtained according to the following expressions:

\[
\text{LogQT} = \alpha + \beta \times \text{Log}\text{RR}
\]

\[
\text{QTci} = \frac{\text{RR}_{1}^{1} \times \text{QT}}{\text{RR}}
\]

where \( \alpha \) is the intercept and \( \beta \) is the slope of linear regression of the log-transformed QT-RR relationship. The individual \( \beta \) was used as the correction coefficient of individual rate-correction formula (QTci). The mean of the \( \beta \) value was 0.5039 ± 0.0217 (0.4557-0.5395).

To evaluate the effects of the test substances, test compound solutions (2 ml/kg) were orally administered to the telemetered animals at around 13:30. The animals were fasted approximately 5 hr before administration and approximately 4 hr after administration. The test drugs and doses administered were astemizole (10 and 30 mg/kg), dl-sotalol (5 and 15 mg/kg), dl-propranolol (30 mg/kg), and nifedipine (30 mg/kg) with at least 1-week interval between administrations of different compounds and different doses. The doses for astemizole and dl-sotalol were determined to exemplify the dose-dependent effects on QT interval, taking into consideration data from a previous study using telemetered cynomolgus monkeys (Ando et al., 2005). The doses of dl-propranolol and nifedipine were selected so that the peak plasma concentration after administration would be over the efficacious concentration in clinic (Rocher et al., 1985; Zybler-Katz et al., 1988). Vehicle controls were administered in the same manner as test compounds. The QT and RR intervals at −2, −1.5, −1 hr pre-dose and 0.5, 1, 2, 4, 7, 12 and 24 hr post-dose were obtained from the analysis of 10 consecutive waves. The heart rate at the same time point was calculated from the RR intervals. The average of the three values at −2, −1.5 and −1 hr pre-dose was used as the baseline.

**Pharmacokinetics**

To determine plasma concentrations of test substances, each test substance was administered orally at each dose to non-telemetered marmosets (250-400 g, 2 males and 2 females). Each animal received the test substance identical to the cardiovascular study design. Approximately 0.15 ml of blood was collected from the tail vein and placed in a heparinized tube at the following time points: 0.5, 1, 2, 4, 7 hr post-dose for astemizole, dl-sotalol and dl-propranolol and 0.25, 0.5, 1, 2, 4 hr post-dose for nifedipine. Plasma samples were obtained after centrifugation and stored at −80°C until determination of plasma concentrations by LC-MS/MS. Desmethy LASTEMZOLE, a metabolite of astemizole that inhibits the rapidly activating delayed rectifier K⁺ currents (I₉) mainly responsible for ventricular repolarization (Vorperian et al., 1996; Zhou et al., 1999), was also measured by LC-MS/MS. The protein binding rates of astemizole, desmethy LASTEMZOLE and dl-sotalol in common marmosets were measured using an equilibrium dialysis method. Plasma samples and isotonic phosphate buffer (100 μl per chamber) were placed in the sample side and dialysis side, respectively, of the wells of a 96-well equilibrium dialysis block (HTD96b, HTDialysis, LLC, Gales Ferry, CT) bisected with a dialysis membrane (MWCO 12-14K, HTDialysis, LLC). After incubation at 37°C for 4 hr, concentrations of the test articles in the plasma (total) and the buffer (unbound) were determined by LC-MS/MS.

**Statistical analysis**

For comparative evaluation of the QT/RR correction methods, linear regression equations for the QTc intervals against RR intervals were obtained by the method of least squares, and the slope and coefficient of variation (CV) of the equations were calculated. When the slope was close to zero, the correction method was considered to have eliminated the effect of heart rate change on the QT interval. In addition, when the CV was less than 10%, the accuracy of the equation was considered appropriate (Matsunaga et al., 1997). The slopes obtained from Bazett’s, Fridericia’s and individual formulas were statistically compared using Tukey’s test after confirming the homogeneity of variance using Bartlett’s test (Bartlett, 1937).

The data for astemizole and dl-sotalol were statistically analyzed for homogeneity of variance using Bartlett’s test (Bartlett, 1937) and were then compared with the time-matched vehicle control values using parametric Dunnett’s test when the variance was homogeneous, or non-parametric Dunnett’s test when the variance was heterogeneous (Dunnett, 1964). The data for dl-propranolol and nifedipine were statistically analyzed for homogeneity of variance by the F-test (JIS, 1965) and then compared with the time-matched vehicle control values using Student’s t-test (JIS, 1965) when the variance was homogeneous, or Welch’s t-test (Welch, 1938) when the variance was heterogeneous.

Values in the data represent the mean ± S.D. of four animals. All statistics were calculated using the SAS system (Version 8.2, SAS Institute, Cary, NC, USA) and values of p < 0.05 were considered significant.
RESULTS

QT-RR relationships and comparative evaluation of QT correction methods

The mean heart rates and mean QT intervals of four common marmosets for 24 hr were 148 ± 10 bpm (407 ± 29 msec for RR interval) and 144 ± 2 msec, respectively. A typical QT-RR relationship in a single subject is given in Fig. 1. The relationship clearly shows positive correlations between QT and RR intervals (slope = 0.1598). Similar observations were also observed in the other three animals. The QT-RR data were expressed as QTc-RR plots from the application of the two generic formulas and individual rate correction (Fig. 2). As shown in Table 1, the slope of the linear regression obtained from individual rate correction (slope = 0.0031) was closer to zero than from Bazett’s (slope = 0.0054) or Fridericia’s (slope = 0.0690). However, the slope from individual correction was significantly different from the slope using Fridericia’s formula but was not significantly different from the one from Bazett’s. All CV values of these linear regressions were within acceptable range (less than 10%). These indicate that the individual correction method showed the most effective independence from the RR interval, even though results from Bazett’s formula were comparable.

![Fig. 1](image1.png)

**Fig. 1.** Typical QT-RR relationship for a single subject. Data points represent QT and RR intervals determined from 10 consecutive ECG waves measured every 6 min over 24 hr. The solid line shows the line of linear regression. The mean heart rate and mean QT interval of this marmoset were 144 beats/min (418 msec for RR interval) and 143 msec, respectively.

![Fig. 2](image2.png)

**Fig. 2.** Corrected QT (QTc) intervals against RR intervals for a single subject (same animal as in Fig. 1). The QT interval was corrected using Bazett’s formula (A), Fridericia’s formula (B), and individual rate correction (C). The solid line shows the line of linear regression.
Effects of QT-prolonging and non-QT-prolonging drugs on heart rate, QT and QTci intervals

Fig. 3 shows representative ECG waveforms recorded before and after the administration of astemizole at 30 mg/kg and Fig. 4 shows time courses for heart rate, QT and QTci interval, and plasma concentration of the test drugs used. None of the vehicle controls used in this study showed effects on the parameters tested, except for transient increases in heart rate and slight shortening of QT interval immediately after administration. Astemizole at 10 and 30 mg/kg significantly prolonged QT interval by 49 and 105 msec, respectively, and QTci interval by 48 and 98 msec, respectively, maximally from the baseline at 2 hr post-dose without affecting heart rate (Fig. 4A). Peak plasma concentrations of astemizole and desmethylastemizole were 0.025 ± 0.018 and 0.268 ± 0.250 μM, respectively, at 0.5 hr after 10 mg/kg administration, and 0.033 ± 0.017 at 0.5 hr and 0.403 ± 0.176 μM at 2 hr, respec-

Table 1. QT interval corrections from Bazett’s and Fridericia’s formulas and individual correction in telemetered common marmosets

<table>
<thead>
<tr>
<th>Parameters*</th>
<th>Bazett</th>
<th>Fridericia</th>
<th>Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>0.0054 ± 0.0092 a</td>
<td>0.0690 ± 0.0135</td>
<td>0.0031 ± 0.0011 ab</td>
</tr>
<tr>
<td>CV (%)</td>
<td>6.5 ± 0.2</td>
<td>6.5 ± 0.2</td>
<td>6.6 ± 0.2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.D. of four animals.
* Slope and CV are the slope and coefficient of variation of the linear regression obtained from the QTc-RR plots for each common marmoset.
+ Significantly different from Fridericia’s formula (P < 0.01) by the Tukey’s test, b Not significantly different from Bazett’s formula (P = 0.9785) by the Tukey’s test, c Statistical analysis was not performed

Fig. 3. Representative ECG traces in a single subject (same animal as in Fig. 1) before (Pre) and 2 hr after oral administration of astemizole at 30 mg/kg. The values of RR and QT intervals are shown on each waveform.
Effectively, after 30 mg/kg administration, dl-Sotalol showed no effect for any parameter at 5 mg/kg, but at 15 mg/kg significantly prolonged QT and QTci intervals by 108 and 80 msec, respectively, maximally from the baseline at 1 hr post-dose with a slight decrease in heart rate (Fig. 4B). Peak plasma concentrations for dl-Sotalol administered at

Fig. 4A. Effects of astemizole (△: 10 mg/kg; ■: 30 mg/kg) (A), dl-sotalol (△: 5 mg/kg; ■: 15 mg/kg) (B) and vehicle control (○) on heart rate, QT interval, and QTci interval. The bottom-most graph shows the plasma concentrations for each test drug. For astemizole, the plasma concentration graph includes desmethylastemizole (Δ: 10 mg/kg; ○: 30 mg/kg). Data points represent the mean ± S.D. of 4 animals. Statistical significance: *p < 0.05 and **p < 0.01 versus time-matched vehicle control group.
5 and 15 mg/kg were 3.90 ± 1.71 and 5.29 ± 2.42 μM, respectively, at 1 hr post-dose. On the other hand, \textit{dl}-Propranolol at 30 mg/kg showed no effect for any parameter tested and the peak plasma concentration was 3.73 ± 2.66 μM at 1 hr post-dose (Fig. 4C), 30.3-fold above the efficacious concentration in clinic (Rocher et al., 1985). Nifedipine at 30 mg/kg significantly increased heart rate (141 bpm above baseline) and shortened QT interval by 41 msec, however, no effect on QTci interval was observed (Fig. 4D). The peak plasma concentration was 1.11 ± 1.52

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4b.pdf}
\caption{Effects of \textit{dl}-propranolol (\textcolor{red}{$\blacktriangle$: 30 mg/kg}) (C), nifedipine (\textcolor{red}{$\blackdiamond$: 30 mg/kg}) (D), and vehicle control (○) on heart rate, QT interval, and QTci interval. The bottom-most graph shows the plasma concentrations for each test drug. Data points represent the mean ± S.D. of 4 animals. Statistical significance: *p < 0.05 and **p < 0.01 versus time-matched vehicle control group.}
\end{figure}
μM at 1 hr post-dose, 5.2-fold above the efficacious concentration in clinic (Zyliber-Katz et al., 1988).

Comparison of QTc interval prolongation in common marmosets with clinical QT prolongation and hERG inhibition

Table 2 shows the plasma concentrations associated with QTc interval prolongation in common marmosets compared with plasma concentrations associated with QT prolongation or TdP in clinic and 50% inhibitory concentrations on hERG. The plasma concentrations of non-QT-prolonging drugs are not shown because no QTc interval prolongation was observed, but hERG inhibitory potential is shown. The plasma concentrations of astemizole (astemizole plus desmethylastemizole) and dl-sotalol associated with QTc interval prolongation in common marmosets were almost consistent with those associated with clinical QT prolongation or TdP. However, free plasma concentrations associated with QTc interval prolongation in common marmosets showed a link with in vitro hERG inhibitory potency for astemizole/desmethylastemizole but not for dl-sotalol.

**DISCUSSION**

The purpose of this study was to determine a suitable QT/RR correction method applicable to common marmoset and to evaluate the predictability of the clinical QT liability of drugs using the present telemetry model. Based on linear regression analysis of QTc interval against RR interval, we found that individual rate correction in accordance with the analysis of covariance (Miyazaki and Tagawa, 2002) best corrected the effect of RR interval on QT interval in comparison with the generic formulas tested. When corrected using the individual correction method, the QT-prolonging drugs tested showed QTc interval prolongation, whereas the non-QT-prolonging drugs did not show QTc interval prolongation, suggesting that the marmoset telemetry model has potential to be utilized in prediction of a drug’s liability to lengthen QTc interval in humans.

Since the ventricular repolarization period varies with heart rate, QT/RR correction formulas such as Bazett’s and Fridericia’s have been widely used to correct the QT interval for the RR interval. However, these standard correction formulas have been shown to have limitations in comparison with the new approach of finding the relationship in an individual (Miyazaki and Tagawa, 2002). As with telemetry studies in other species (Miyazaki and Tagawa, 2002; Kano et al., 2005; Holzgrefe et al., 2007), with common marmosets the individual method showed better corrections than both traditional formulas, although the corrections from Bazett’s were nearly comparable. Nifedipine, which has no QT-prolonging risk in clinic, was reported to cause tachycardia and false QTc interval prolongation in a canine telemetry study using Fridericia’s formula (Toyoshima et al., 2005). Verapamil, another

Table 2. Plasma concentrations of test drugs associated with QT prolongation in common marmosets and humans, including hERG channel inhibition

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Total (μM)</th>
<th>Unbound (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma conc. at QT prolongation in marmosets</td>
<td>Plasma conc. at clinical QT prolongation/TdP</td>
</tr>
<tr>
<td>Astemizole combined2</td>
<td>0.293</td>
<td>0.134-0.545* b</td>
</tr>
<tr>
<td>Astemizole</td>
<td>0.025</td>
<td>ND</td>
</tr>
<tr>
<td>Desmethylastemizole</td>
<td>0.268</td>
<td>ND</td>
</tr>
<tr>
<td>dl-Sotalol</td>
<td>5.29</td>
<td>5.54 c</td>
</tr>
<tr>
<td>dl-Propranolol</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*: No QT prolongation, ND: No data available
b: Calculated using protein binding rate in the common marmoset for astemizole (98.7%), desmethylastemizole (96.5%), and dl-sotalol (5.7%) c: Astemizole plus desmethylastemizole d: Molar concentration was calculated using the molecular weight of astemizole e: Includes previously reported data, f: Hoppa et al. 1991 and Savic et al. 1993, g: Kimura et al. 1996, h: Zhou et al. 1999, i: Kirsch et al. 2004, j: Kawakami et al. 2006, k: Zhang et al. 1999
er calcium channel blocker, also caused tachycardia and false QT-prolonging results in the same canine study (Toyoshima et al., 2005) and in a monkey study using Bazett’s formula (Ando et al., 2005). The explanation given for the QTc overestimations was that the heart rate was out of a valid correction range due to hyper-tachycardia (130-170% of baseline value) (Ando et al., 2005; Toyoshima et al., 2005). Contrary to those studies and with the use of individual correction, nifedipine showed no QTc interval prolongation, although it did cause hyper-tachycardia (210% of baseline value). These findings strongly support the utility of the individual correction method.

Astemizole at 10 mg/kg and dl-sotalol at 15 mg/kg significantly prolonged QTc interval with peak plasma concentrations of 0.293 (astemizole plus desmethylastemizole) and 5.29 μM, respectively. We used the combined plasma concentrations of astemizole and desmethylastemizole for comparison with clinical outcomes because desmethylastemizole was reported to have almost the same potential as astemizole for I_k/hERG blockade and action potential prolongation (Vorperian et al., 1996; Zhou et al., 1999). The plasma concentrations of astemizole and dl-sotalol in common marmosets were similar to those in humans associated with QT prolongation/TdP (0.134-0.545 and 5.54 μM, respectively) (Hoppu et al., 1991; Saviuc et al., 1993; Kimura et al., 1996), suggesting that sensitivity of common marmosets is appropriate for predicting drug-induced QT interval prolongation in clinic.

Since the blockade of I_k encoded by hERG appears to be the main mechanism of drugs that prolong QT interval (Redfern et al., 2003), assessments on hERG have been widely performed for QT screening. It was reported that the IC_{50} values in the hERG/I_k assay correlate well with the free plasma concentrations associated with QT interval prolongation (Webster et al., 2002). Indeed, the free plasma concentrations of astemizole and desmethylastemizole associated with QTc interval prolongation in this study were 0.3 and 9 nM, respectively, which were close to hERG IC_{50}s of 0.9 and 1 nM, respectively (Zhou et al., 1999). On the other hand, dl-sotalol has very weak hERG inhibitory potential with an IC_{50} value of 278 μM (Kirsch et al., 2004), but apparently caused QTc interval prolongation at the free plasma concentration of 4.99 μM in common marmosets. dl-Sotalol also prolonged QTc intervals at a free plasma concentration of 7.2 μM in anesthetized dogs (Schnelle and Garrett, 1973; Tabo et al., 2006) and 5.3 μM in humans (Carr et al., 1995; Kimura et al., 1996). The reason why dl-sotalol shows such weak hERG blockade even though it prolongs QT interval via the I_k blockade (Antonaccio and Gomoll, 1993) is unclear, but it is considered that the QT-prolonging effect of dl-sotalol might be caused, at least partially, through a mechanism other than direct hERG inhibition. Contrary to the case of dl-sotalol, dl-propranolol showed no QTc interval prolongation even though it has apparently stronger potential than dl-sotalol to inhibit hERG (IC_{50} = 3.9 μM) (Kawakami et al., 2006). It was reported that dl-propranolol inhibits not only I_k/hERG but also I_n (Varro et al., 1990), leading to a shortening of APD in isolated guinea pig papillary muscles at 3 μM and above (Hayashi et al., 2005) or no effect on QTc interval, as in the present study, in conscious dogs up to 30 mg/kg (Toyoshima et al., 2005). These findings suggest that drugs that may have QT-prolonging mechanisms other than hERG blockade or inhibit not only hERG but also other ion channels might show discrepancies between hERG inhibitory potential and actual QT interval prolongation, indicating that a ventricular repolarization study would be needed for accurate evaluation of the QT liability of drugs. In fact, the International Conference on Harmonization S7B guideline (ICH S7B guideline) requires not only in vitro hERG studies but also in vivo QT studies for the assessment of the potential risk of QT interval prolongation.

The present study has some limitations. Both RR and QT intervals fluctuated throughout 24 hr as shown in Fig. 1. Horii et al. (2002) showed that common marmosets have diurnal changes in heart rate and so the variation of the RR interval was probably caused by circadian rhythm. The QT fluctuation at the same RR interval has also been observed in other species such as dogs, pigs and humans (Harada et al., 2005; Kano et al., 2005; Malik et al., 2002) and might also be caused by circadian rhythm (Sarma et al., 1990) or by changes in autonomic nervous activity (Harada et al., 2005). To minimize the potent influences of circadian rhythm, drug effects were compared with a time-matched vehicle control in this study. The maximum difference of QTci interval at almost the same RR interval was about 30 msec (Fig. 2C), whereas the statistically significant but minimum difference of QTci interval between vehicle control and astemizole at 10 mg/kg or dl-sotalol at 15 mg/kg was at least 30 to 40 msec (Figs. 4A and 4B). Therefore, the statistically significant detection in this study was beyond the QTci variation, indicating that the QT fluctuation observed in this study would not affect the present outcome. Another limitation is that the current study evaluated the combined results obtained from both genders (2 males and 2 females). Since women are considered more sensitive to drug-induced QT interval prolongation than men in clinic (Reinoehl et al., 1996; Benton et al., 2000), gender difference may have affected
the present results. However, there were no marked differences between males and females concerning the QT-prolonging responses of astemizole and dl-sotalol in this study (individual data not shown). Therefore, the combination of data from both genders would not affect the conclusion of this study although further studies regarding gender difference are highly recommended.

In conclusion, the test drugs used in this study clearly demonstrated reactivity consistent with clinical outcome in common marmosets when the individual QT/RR correction method was applied. In addition, because of the small size of the animal, only small amounts of test drugs are required. Therefore, the present telemetry study is considered useful and cost-effective for the prediction of clinical QT-prolonging potential of drugs in the early stages of drug development.

ACKNOWLEDGMENT

We gratefully thank Dr. Sigeo Ito from Hokkaido University for his excellent advice concerning this article.

REFERENCES


Omata, T., Kasai, C., Hashimoto, M., Hombo, T. and Yamamoto, K.
QT interval prolongation in common marmosets.


Welch, B.L. (1938): The significance of the difference between two means when the population variances are unequal. Biometrika, 29, 350-362.

