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RESEARCH PAPER

Dose–response effects of sotalol on cardiovascular function in conscious, freely moving cynomolgus monkeys

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Background and purpose: The non-selective β-adrenoceptor antagonist, D,L-sotalol (sotalol) is commonly employed as a positive control during preclinical cardiovascular safety pharmacology testing, mainly because of its ability to prolong QT interval duration. However, no information appears in the literature, except in abstract form, regarding the dose–response effects of sotalol in unanesthetized monkeys. The current study was conducted to determine the dose– and plasma–response effects of orally administered sotalol on cardiovascular function in conscious non-human primates.
Experimental approach: Male cynomolgus monkeys were implanted with telemetry devices and the effects of sotalol hydrochloride (5, 10 and 30 mg kg^{-1} of body weight, p.o.) on arterial blood pressure, heart rate, body temperature and electrocardiogram waveform were continuously monitored for 6 h after dosing. Blood was sampled for the measurement of plasma concentrations of sotalol.
Key results: Sotalol dose dependently decreased heart rate and prolonged RR, PR, QT and corrected QT intervals, while having little or no effects on the QRS complex, arterial pressure or body temperature, over the dose range tested. When the data were related to plasma concentrations of sotalol, it was clear that the cardiovascular effects occurred in a similar pattern and to a comparable degree as those reported in human studies.
Conclusions and implications: The current study helps demonstrate the validity of utilizing telemetry-instrumented non-human primates for the cardiovascular safety pharmacology assessment of drugs prior to first-in-human testing, and its findings may serve as a reference source for the dose– and plasma–response effects of orally administered sotalol in conscious monkeys.
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Keywords: arterial blood pressure; body temperature; cardiovascular; electrocardiogram; heart rate; monkey; QT prolongation; safety pharmacology; sotalol; telemetry

Abbreviations: DAP, diastolic arterial blood pressure; ECG, electrocardiogram; IACUC, Institutional Animal Care and Use Committee; ICH, International Conference on Harmonisation; MAP, mean arterial blood pressure; QTc, corrected QT; SAP, systolic arterial blood pressure; sotalol, D,L-sotalol

Introduction

For several decades, the non-selective β-adrenoceptor antagonist, sotalol has been clinically utilized for its antihypertensive and antiarrhythmic properties. However, at higher doses and in patients with select, pre-existing medical conditions such as long QT syndrome and renal impairment, sotalol can prolong cardiac action potential duration to such an extent that torsades de pointes may result (Kehoe *et al.*, 1993; Cammu *et al.*, 1999; Lehtonen *et al.*, 2007).

The effects of sotalol on cardiovascular function have been extensively studied in anaesthetized animals where it has been reliably demonstrated that the drug can produce bradycardia and prolong QT interval in most species (Gomoll *et al.*, 1990; Mittelstadt *et al.*, 1997; Sakaguchi *et al.*, 2005). In addition, with the improvement of telemetry technology and due to the International Conference on Harmonisation (ICH) recommendations to utilize unanesthetized animals

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for the safety pharmacology testing of drug candidate compounds (US FDA, 2001), a number of laboratories have begun to publish dose–response data for sotalol in conscious, freely moving animals. For example, in guinea pigs that had previously been instrumented with telemetry devices, oral administration of sotalol dose dependently induced hypotension and increased both RR and corrected QT (QTc) intervals, significantly at 100 mg kg^{-1} (Hess *et al*., 2007). In telemetry-instrumented dogs, administration of sotalol at doses of 4–32 mg kg^{-1}, p.o., decreased heart rate and prolonged QTc interval in a relatively dose-dependent manner (Batey and Doe, 2002).

Historically, the dog has been the most frequently utilized species for safety pharmacology studies when large animals were required (Authier *et al*., 2007a). However, because human pharmacokinetics and metabolism of drugs can often be more similar to that in non-human primates than in dogs, the use of monkeys for cardiovascular safety assessment has increased (Zuber *et al*., 2002; Ward and Smith, 2004). Although non-human primates are one of the most frequently used species for studies of preclinical safety (Chaves *et al*., 2006) and in spite of the fact that sotalol is a common positive control in preclinical cardiovascular studies (Sasaki *et al*., 2005), no full publication has appeared in the literature in which the cardiovascular effects of orally administered sotalol were dose dependently assessed in conscious monkeys.

In the present study, male cynomolgus monkeys were implanted with telemetry devices, and the effects of sotalol hydrochloride (5, 10 and 30 mg kg^{-1} of body weight, p.o.) on arterial blood pressure, heart rate, body temperature, and electrocardiogram (ECG) waveform were continuously monitored. Methodology was comparable to that utilized by Ando *et al*. (2005), who reported dose–response effects for a number of other (non-sotalol) compounds that prolonged QTc interval, except that the potentially complicating factor of body temperature was probably not assessed in the latter study, as no such measurement was reported. Cardiovascular results from the current study were similar to those reported in humans when plasma levels of sotalol were compared. The present study may serve as a useful reference for the dose- and plasma-related effects of sotalol on cardiovascular function as well as add support for the use of telemetry-instrumented cynomolgus monkeys for safety pharmacology assessment prior to testing in humans.

Methods

Animals and dosing

The study was approved by the Institutional Animal Care and Use Committee (IACUC) of Maccine Pte Ltd. Four young male cynomolgus monkeys (*Macaca fascicularis*) were chosen from a stock colony previously obtained from Pusat Studi Satwa Primata (Primate Research Center) at the Institut Pertanian Bogor (Indonesia). No significant gender-related differences were expected during the conduct of the study; therefore, only male monkeys were used to conserve animals. Prior to the study, the animals were physically examined and blood was sampled for clinical pathology to confirm suitability of the primates for experimental use. The animals were group-housed in an air-conditioned facility, with a 12-h light–dark cycle (lights on at 0700 hours, off at 1900 hours), at Maccine Pte Ltd. The temperature range was 19.6–25.0 °C and the relative humidity range was 63–84% for the duration of the study. Water was available *ad libitum* and the animals were fed (twice daily) a diet of monkey chow free of animal protein (Primate Lab Diet 5048; Purina Mills, St Louis, MO, USA). Fruits were offered twice daily in controlled amounts.

Prior to each dosing, the animals were fasted overnight and were fed approximately 4 h after the start of dosing. Fasted body weights of the animals ranged between 2.5 and 3.5 kg throughout the study period. Using a Latin square design with a minimum of a 3-day washout period between doses, the same four animals were orally administered doses of 0 (vehicle control), 5, 10 and 30 mg kg^{-1} of sotalol hydrochloride. After each dose and prior to removal of the gavage tube, the tube was flushed with 10 mL of purified water. The observer was unaware of the dose each animal received. Sotalol hydrochloride (manufactured at Abbott Laboratories) was formulated fresh daily, in sterile water, and was administered at a dosing volume of 2 mL kg^{-1} of body weight.

Surgical procedures

Prior to the day of their surgery, the animals were food deprived overnight. On the day of surgery, in preparation for inhalation anaesthetic, the animals were sedated with ketamine (5–15 mg kg^{-1}, i.m.) and atropine sulphate (0.04–0.06 mg kg^{-1}, i.m.) was also administered. Isoflurane (4% in oxygen for induction, 0.5–2% for maintenance) was utilized as the anaesthetic throughout the surgical procedure. Core body temperature was maintained with a homeothermic blanket system that was thermostatically controlled (activated at <37 °C) by means of a rectal thermocouple. Fluid replacement was provided throughout the surgical procedure with approximately 10 mL kg^{-1} h^{-1} of lactated Ringer's solution. The incision areas were shaved and scrubbed with a proprietary skin-sterilizing agent and with ethanol. Following surgery, the animals were singly housed for up to 2 weeks and then returned to their group-housed cages.

To implant the telemetry transmitter (model number TL11M2-D70-PCT; Data Sciences International, St Paul, MN, USA), a scalpel incision was made through the skin in the abdominal midline such that the opening was just large enough to insert the implant body. A corresponding midline incision was made in the abdominal muscle, and the implant body was inserted. The implant was sutured to the abdominal wall, intraperitoneally, using the suture tabs on the implant.

For arterial cannulation, an incision was made through the skin, high on the ventral surface of either leg along the femoral groove, to locate and to isolate the femoral artery. A trocar was then used to tunnel under the skin from the ventral surface of the leg to the abdominal incision site. The arterial blood pressure catheter was passed through the trocar, and the catheter was introduced into the femoral

artery until its tip was estimated to be in the terminal portion of the abdominal aorta. It was then secured in place by suture ties, and Vetbond (3M Company; St Paul, MN, USA) was also applied over the suture ties on the artery. Additional securing sutures were placed along the length of the exposed catheter up to the abdomen.

The ECG leads were implanted by making two small scalpel incisions through the skin, one at the left lateral thorax just anterior to the last rib and the other at the right thoracic inlet. A trocar was used to tunnel subcutaneously from the midline abdominal incision to these two sites, and the positive and negative ECG leads were passed to the incision sites on the left and right, respectively. Three to four centimetres of silicone tubing was removed from the end of both leads, and the exposed stainless steel wires of each were made into single loops. Each loop was then secured in its respective location under the surface of the muscles. The overlying muscles and skin incisions were closed using absorbable suture material, and Vetbond was applied to some of the skin incision sites.

Telemetry recordings and data analysis

For telemetry recordings, the primates were placed into individual recording cages to acclimate for at least 90 min prior to the start of baseline recordings, and the primates were allowed free movement within the cage for the duration of each study period. Each recording cage was equipped with a Data Sciences receiver (model number RMC-1) and was separated from other cages sufficiently to prevent cross talk. Data Sciences OpenART software (version 3.11) provided a direct digital interface with a NOTOCORD-hem data acquisition and analysis system (version 4.2.0.128; NOTOCORD Systems SAS, Croissy Sur Seine, France).

Prior to each dosing, data collection commenced 60 ± 4 min beforehand and ended 6 ± 0.1 h after dosing. Systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), heart rate and the lead II ECG parameters were continuously assessed. Mean arterial blood pressure (MAP) was calculated as DAP + 1/3 (SAP – DAP). In addition to body temperature, the following lead II ECG parameters were measured: RR interval, PR interval, QRS duration, QT interval and QTc interval (calculated as $QTc = QT/\sqrt[3]{RR}$, by the method of Fridericia (1920) and Authier *et al*. (2007b). The telemetry data acquired following treatment with sotalol were compared with data from the corresponding time points following vehicle treatment using an ANOVA with repeated measures and followed by a Dunnett *post hoc* test (GraphPad Prism, v 4.03). Changes were considered to be statistically significant at $P<0.05$. Arrhythmias were characterized based on visual comparison of the study's ECG waveforms to a normal ECG waveform.

Measurement of sotalol levels in blood plasma

After 3 ± 0.2 h from the start of dose administration, whole blood samples (5 mL) were collected via needle stick from the femoral vein of each animal and put into sodium heparinized blood collection tubes. A 3-h blood collection time point was chosen so as not to interfere with cardiovascular data monitoring during the maximal cardiovascular effects of sotalol (approximately 2 h post dosing) yet still have relatively high plasma concentrations remaining (Carr *et al*., 1992; Sasaki *et al*., 2005). Plasma was separated (2700 *g* for 10 min at 4 °C) and then stored at approximately −20 °C until analysis of sotalol concentrations by liquid–liquid extraction HPLC tandem mass spectroscopy.

Results

In the conscious, freely moving, telemetry-instrumented monkeys, sotalol hydrochloride (5, 10 and 30 mg kg^{-1}, p.o.; administered according to a Latin square design) had no statistically significant effects on SAP, DAP and MAP (Figure 1). However, an approximately 10–20% trend towards hypotension was observed for all three measures

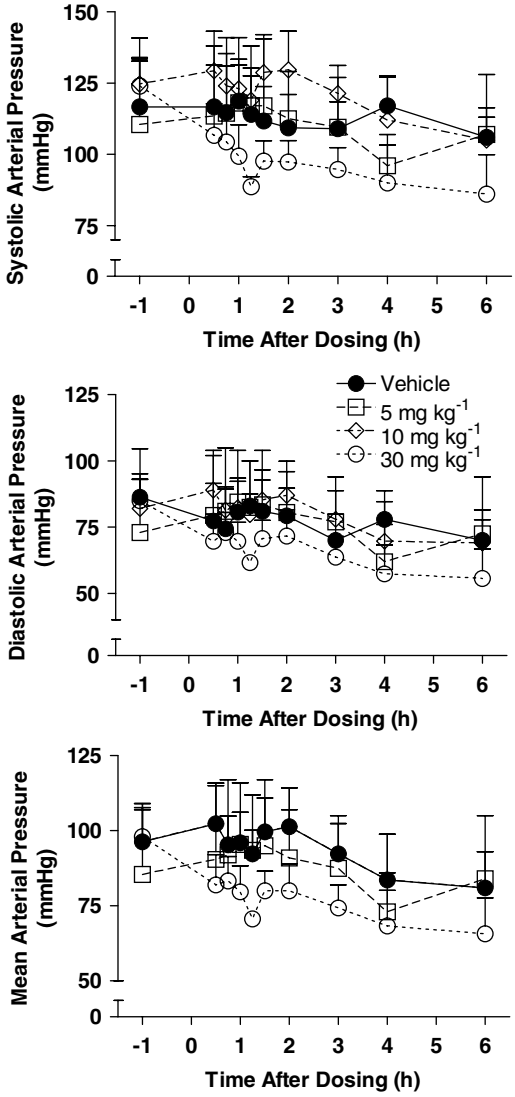

Figure 1 Sotalol (D,L-sotalol; 5–30 mg kg^{-1}, p.o.) did not statistically significantly alter systolic (SAP), diastolic (DAP) and mean arterial blood pressures (MAP) in conscious, freely moving cynomolgus monkeys. Mean ± s.e.mean; $n = 4$ animals per treatment.

with the 30 mg kg^{-1} dose throughout most of the 6-h post-dosing interval. In contrast, dose-related, statistically significant bradycardia was observed at all three doses from 30 min to 6 h after administration, with a maximal effect of an approximately 50% reduction in heart rate at 30 mg kg^{-1} (Figure 2). There were no effects on body temperature (Figure 2).

Electrocardiogram was also monitored in the telemetry-instrumented primates. Sotalol elicited a transient, dose-independent prolongation of the QRS complex duration at 1.5 h post dosing ($P<0.05$; approximately 3 ms) (Figure 3). PR, RR, QT and QTc intervals were all significantly prolonged over most of the 6-h post-dosing monitoring period (Figures 3 and 4). For PR interval duration, the degree of prolongation (approximately 10–15 ms) was fairly comparable at all three doses and at all post-dosing time points tested. For RR interval, prolongation was more dose related, with statistically significant effects occurring during at least one time point for all three doses tested, and with maximal increases of approximately 330 ms at the 30 mg kg^{-1} dose from 1 to 3 h after administration. QT interval was significantly prolonged at all post-dosing time points with the dosage of 30 mg kg^{-1} (maximal increase of approximately 260 ms), and a non-statistically significant increase of approximately 50–100 ms was observed at most time points with the doses of 3 and 10 mg kg^{-1}. For the heart rate corrected QT (QTc) interval, a similar pattern of effects was seen, but with statistically significant prolongation occurring for both the 10 and 30 mg kg^{-1} treatments.

Visual assessment of the ECG traces disclosed no increases in aberrant waveforms after dosing with either 5 or

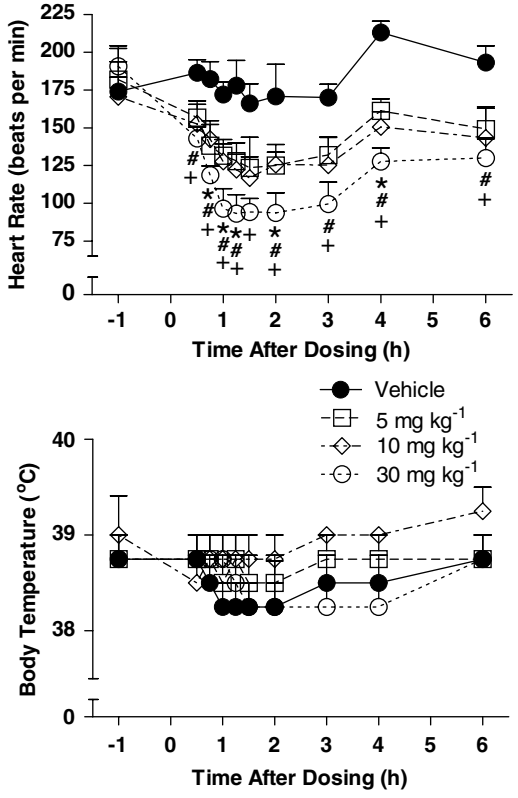

Figure 2 Sotalol (D,L-sotalol; 5–30 mg kg^{-1}, p.o.) dose dependently induced bradycardia but had no effect on body temperature. Statistically significant decreased heart rate occurred at all doses tested for up to 6 h post dosing, with a maximal decrease between approximately 1–3 h after dosing, and with approximately 50% bradycardia following the 30 mg kg^{-1} dose. Mean ± s.e.mean; $n=4$ animals per treatment. $^{*}P<0.05$ for the comparison of 5 mg kg^{-1} with vehicle control at corresponding time points; $^{\#}P<0.05$ for 10 mg kg^{-1} vs vehicle control; and $^{+}P<0.05$ for 30 mg kg^{-1} vs vehicle control.

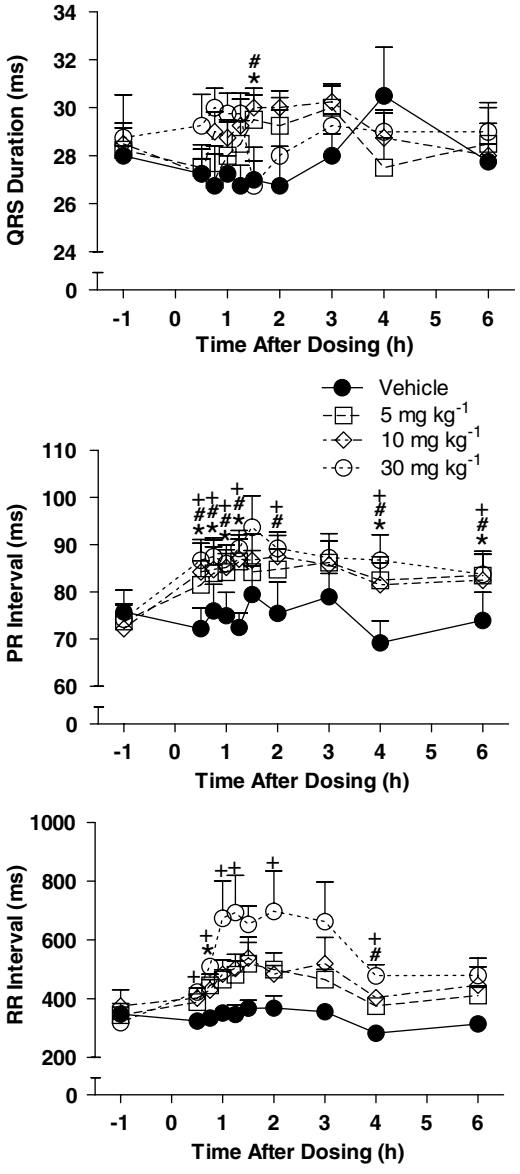

Figure 3 Sotalol (D,L-sotalol) prolonged both RR and PR intervals over most of the 6 h post-dosing monitoring period, but it had little to no effects on the QRS complex. QRS duration was significantly prolonged (by approximately 3 ms) only at 90 min after administration of 5 or 10 mg kg^{-1} of sotalol, p.o.; no significant effects were observed at 30 mg kg^{-1}. PR interval was significantly prolonged by approximately the same duration (10–15 ms) at all three doses tested. RR interval was increased by sotalol (maximum of approximately 330 ms), with statistically significant effects occurring during at least one time point at all doses tested. Mean ± s.e.mean; $n=4$ animals per treatment. $^{*}P<0.05$ for the comparison of 5 mg kg^{-1} with vehicle control at corresponding time points; $^{\#}P<0.05$ for 10 mg kg^{-1} vs vehicle control; and $^{+}P<0.05$ for 30 mg kg^{-1} vs vehicle control.

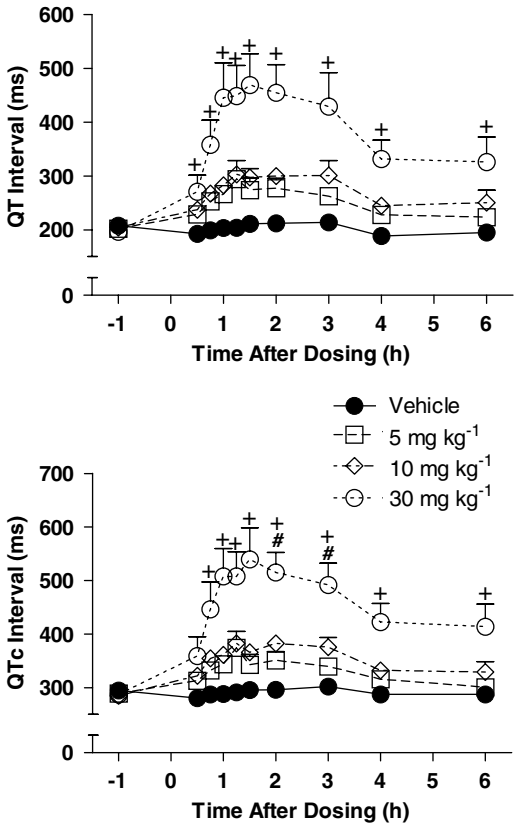

Figure 4 Sotalol (D,L-sotalol) dose dependently prolonged QT interval over the dose range of 5–30 mg kg^{-1}, p.o., at all post-dosing time points tested. For uncorrected QT interval, the effects were statistically significant only at the highest dose tested, 30 mg kg^{-1}, p.o., but a non-statistically significant prolongation of approximately 50–100 ms was observed at the doses of 5 and 10 mg kg^{-1}. For corrected QT (QTc) interval, data were significant with the doses of 10 and 30 mg kg^{-1}. Mean ± s.e.mean; $n=4$ animals per treatment. $^{\#}P<0.05$ for the comparison of 10 mg kg^{-1} with vehicle control at corresponding time points; and $^{+}P<0.05$ for 30 mg kg^{-1} vs vehicle control.

10 mg kg^{-1} sotalol, relative to that with vehicle control. In contrast, a relatively high incidence of aberrant waveforms was observed after treatment with the highest dose, 30 mg kg^{-1}. These abnormal waveforms included aberrations mainly consistent with multifocal ventricular premature contractions. However, signs of ventricular tachycardia, third-degree atrioventricular block and atrial premature complexes were also present.

In blood samples obtained from these same animals at 3 h after dosing with sotalol, an approximately linear relationship was observed between the doses administered and the resultant plasma concentrations. Plasma levels of sotalol were 0.85 ± 0.08, 1.63 ± 0.10 and 5.90 ± 0.59 μg mL^{-1} (mean ± s.e.mean) for the doses of 5, 10 and 30 mg kg^{-1}, p.o., respectively.

Discussion and conclusion

Sotalol was originally manufactured for use as an antihypertensive agent but was later approved for the treatment of atrial and ventricular arrhythmias (Anderson and Prystowsky, 1999). In normotensive individuals, sotalol typically has little to no effect on blood pressure while still reducing heart rate (Antonaccio and Gomoll, 1990). The bradycardia induced by sotalol generally occurs at plasma concentrations lower than those resulting in a significant prolongation of QTc interval. For example, an approximately three-fold safety margin was found in patients with chronic, high-frequency ventricular arrhythmias in that the plasma concentration of sotalol associated with a 50% reduction of the maximal slowing in exercise-induced heart rate was 0.8 μg mL^{-1}, whereas 2.6 μg mL^{-1} was the plasma concentration associated with a significant increase in QTc interval duration (Wang *et al*., 1986). Nevertheless, at the higher end of effective doses (that is, greater than approximately 300–400 mg day^{-1}), and in people with particular conditions, such as acquired long QT syndrome and renal impairment, sotalol can sufficiently prolong cardiac action potential duration so that torsades de pointes may result (Kehoe *et al*., 1993; Anderson and Prystowsky, 1999; Cammu *et al*., 1999; Lehtonen *et al*., 2007).

In preclinical cardiovascular safety pharmacology studies, sotalol is commonly employed as a positive control (Sasaki *et al*., 2005). Its effects have been extensively studied in anaesthetized animals where it has reliably been demonstrated that sotalol can produce bradycardia and prolong QT interval in most species (Gomoll *et al*., 1990; Mittelstadt *et al*., 1997; Sakaguchi *et al*., 2005). However, because of the potential for anaesthetic effects, the use of conscious animals is often preferable and is, therefore, recommended in the ICH Guidelines for safety pharmacology testing (US FDA, 2001; Hamlin *et al*., 2003; Sakaguchi *et al*., 2005; Takahara *et al*., 2005). In addition, cardiovascular data from unrestrained (that is, freely moving) animals are recommended, because it can avoid constraint-induced stress responses better (US FDA, 2001). Furthermore, because the pharmacokinetics of all drugs are dependent on dosing route, the clinical route of administration (primarily oral for sotalol) is recommended for use during preclinical studies (US FDA, 2001).

Oral administration of sotalol to conscious, freely moving animals has consistently been demonstrated to prolong QTc interval, but with some differences in its effective dose range between species. In guinea pigs, a single administration of sotalol (10, 30 or 100 mg kg^{-1}, p.o.) dose dependently increased QTc interval duration, but with a statistically significant effect only at the 100 mg kg^{-1} dose (Hess *et al*., 2007). In miniature pigs, the only dose of sotalol tested (10 mg kg^{-1}, p.o.) significantly prolonged QTc (Kano *et al*., 2005). In dogs, 4–32 mg kg^{-1} of sotalol, p.o., prolonged QTc interval in a dose-dependent manner (Batey and Doe, 2002; Lake-Bruse *et al*., 2004). In cynomolgus monkeys, when the effects of sotalol (5 mg kg^{-1}, p.o.) were compared among several different testing facilities, prolongation of QTc interval was observed in all seven studies; however, these effects were statistically significant in only two out of the seven test groups (Sasaki *et al*., 2005). In the present study in cynomolgus monkeys, dose-dependent QTc prolongation occurred over the dose range of 5–30 mg kg^{-1}, p.o., with statistically significance at the doses of 10 and 30 mg kg^{-1}. It should be noted that despite this significant prolongation in

QTc interval duration with the two highest doses, only the 30-mg kg^{-1} treatment group exhibited an increased incidence of arrhythmias relative to vehicle control treatment.

The degree of sotalol-induced QTc interval prolongation that occurred during the present study was similar, when compared relative to plasma levels, to that reported after exposure in humans. In the monkeys of the current study, maximal QTc interval prolongation was 83, 91 and 244 ms (or 29, 31 and 83%, respectively) for the respective doses of 5, 10 and 30 mg kg^{-1}, p.o., with mean plasma concentrations of 0.85, 1.63 and 5.90 μg mL^{-1}. In human volunteers, maximal QTc interval prolongation was approximately 30, 50 and 100 ms (or approximately 8, 14 and 27%, respectively) after single-dose oral administration of 80, 160 and 320 mg of sotalol, which corresponded to mean peak plasma concentrations of 0.63, 1.12 and 2.33 μg mL^{-1}, respectively (Le Coz *et al*., 1992). In patients receiving daily sotalol treatment, a positive linear relationship was found between plasma sotalol concentrations and changes in QTc duration such that, for example, an average plasma concentration of sotalol of 4.0 μg mL^{-1} correlated with a mean increase in QTc interval of 14% over baseline (Wang *et al*., 1986). By comparison, in conscious dogs, a 17% prolongation in QTc interval (that is, a mean QTc interval duration of 296 ms, as compared with 254 ms for vehicle control) was produced at a much higher mean plasma concentration (71 μg mL^{-1}; Vormberge *et al*., 2006). Statistically significant QTc prolongation was not observed in conscious dogs at plasma levels of 1.0 and 4.5 μg mL^{-1}, concentrations that were similar to those prolonging QTc interval duration in the present study in conscious monkeys (1.63 and 5.90 μg mL^{-1}; Gomoll *et al*. 1990; Vormberge *et al*., 2006).

In addition to its comparable effects on QTc interval duration in humans and monkeys, sotalol produces parallel effects on a number of other ECG measures. In cardiac patients, sotalol has been found to prolong both PR and RR intervals while having minimal or no effects on QRS duration over the plasma concentration range of approximately 1–6 μg mL^{-1} (McComb *et al*., 1987; Sahar *et al*., 1989). In human volunteers administered a single dose of 160 or 320 mg of sotalol, p.o., RR interval duration was prolonged; PR interval and QRS complex duration data were not reported (Fossa *et al*., 2007). In the monkeys utilized in the current study, both PR and RR intervals were significantly prolonged over the dose range of 5–30 mg kg^{-1}, p.o. (mean plasma concentrations of 0.85–5.90 μg mL^{-1}, respectively), with minimal to no effects ($\leqslant$3 ms reduction) on QRS duration.

Another parallel, between humans and monkeys, occurs with the effects of sotalol on heart rate and arterial pressure. After oral administration to normotensive humans, sotalol (plasma concentration range approximately 0.5–5 μg mL^{-1}) generally produces bradycardia while having little to no effects on blood pressure; an approximately 40% reduction in exercise heart rate occurred at a mean plasma concentration of 5 μg mL^{-1} (Antonaccio and Gomoll, 1990). In the present study, sotalol produced significant decreases in heart rate at doses of 5, 10 and 30 mg kg^{-1}, with maximal efficacy of an approximately 50% decrease at 30 mg kg^{-1} (5.90 μg mL^{-1}). Whereas arterial pressure was not also significantly affected, an approximately 10–20% trend towards hypotension was observed at the highest dose tested (30 mg kg^{-1}, p.o.). It should be noted that statistical power for the treatment size (that is, $n=4$ animals) utilized in this study is such that an approximately 25% difference vs control data is necessary to result in statistical significance ($P<0.05$) for a given treatment. Therefore, should a larger number of animals be tested, sotalol may result in a statistically significant reduction in arterial pressure in monkeys at the dose of 30 mg kg^{-1} (5.90 μg mL^{-1}).

In summary, the present study demonstrated that in conscious, freely moving cynomolgus monkeys, sotalol hydrochloride (5, 10 and 30 mg kg^{-1} of body weight, p.o.; administered in a Latin square design with a 3-day washout period) dose dependently decreased heart rate and prolonged PR, PR, QT and QTc interval durations, while having little to no effects on the QRS complex, arterial blood pressure or body temperature. Similar effects are reported both in human volunteers and in cardiac patients at comparable plasma levels of sotalol. The current findings add justification to the more frequent use of telemetry-instrumented monkeys during preclinical safety pharmacology testing. The study results may also serve as a source of data regarding the dose– and plasma–response effects of sotalol on cardiovascular function in non-human primates.

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Conflict of interest

JJ Lynch III, LE Hernandez, RA Nelson, KC Marsh, BF Cox and SW Mittelstadt are employees of Abbott Laboratories. The cardiovascular portion of the study was conducted at Maccine Pte Ltd with financial support from Abbott Laboratories.

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