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# Measurements of blood pressure and electrocardiogram in conscious freely moving guineapigs: a model for screening QT interval prolongation effects

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## Summary

The pro-arrhythmic risk inherent to a new drug must be assessed at an early preclinical stage. Telemetry system implantation is a method widely used *in vivo* in various species. The present study was designed to assess whether conscious freely moving guineapigs can be used to predict QT prolongation *in vivo*. The guineapig has three advantages over the dog and the primate. First, it has specific ion channels similar to man; second, a smaller amount of test article is required for the investigation and third, its housing is less expensive. Under sterile conditions and isoflurane anaesthesia, telemetry transmitters were implanted intraperitoneally in male Dunkin Hartley guineapigs. Blood pressure, heart rate and electrocardiographic intervals were measured from two days up to eight months. Chronic implantation of the telemetry device did not lead to anatomic or macroscopic alterations in the abdominal cavity and no inflammation of the peritoneum or infection was observed. Four reference compounds were used: three positive (sotalol, terfenadine and dofetilide) and one negative reference (enalapril). Single oral administration of all three positive references dose-dependently induced bradycardia and QT corrected (QTc) prolongation. In contrast, neither enalapril nor its vehicle prolonged the QTc. These results demonstrate that the guineapig is both a suitable model and a good alternative to dogs or primates to assess the potential of compounds for QT interval prolongation in the early stages of drug development.

**Keywords** QT prolongation; ECG intervals; telemetry; conscious guineapig

In electrocardiography, the QT interval is a measure of the duration of ventricular depolarization and repolarization. In the past few years, drug-induced QT prolongation, potentially leading to ventricular arrhythmia, such as torsades de pointes, has drawn increasing attention from health authorities and drug developers. Several drugs such as terfenadine, grepafloxacin and cisapride were withdrawn from the market because they either directly caused electrocardiographic

(ECG) changes and/or resulted in a drug–drug interaction that led to unacceptable cardiotoxicity (Haverkamp *et al.* 2000, Crouch *et al.* 2003, Katchman *et al.* 2006). As a result, the International Conference on Harmonization (ICH) published two guidance for industry, ICH S7A 'Safety Pharmacology Studies for Human Pharmaceuticals' and ICH S7B 'The Non Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT interval prolongation) by Human Pharmaceuticals' (ICH 2000, 2005). These guidances are intended to help protect

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clinical trial participants and patients from potential adverse effects of pharmaceuticals. Electrophysiological *in vitro* assays are commonly used in the pharmaceutical industry to examine drug effects on the human ether-a-go-go-related gene (hERG) channel. However, the predictive value of these studies is limited, verapamil being a notable example of a false-positive. Verapamil blocks the hERG K<sup>+</sup> channel, but is reported to have no potential to generate torsades de pointes (Chouabe *et al.* 1998, Redfern *et al.* 2003, Schneider *et al.* 2005). To assess proarrhythmic risk, ICH S7B guidance suggests, in addition to the hERG channel assay, to measure blood pressure (BP), heart rate, and ECG intervals in an *in vivo* model. Several models have been developed to measure BP and ECG intervals in anaesthetized guineapigs (Noda & Hashimoto 2004, Testai *et al.* 2004, Hauser *et al.* 2005) and in conscious, freely moving dogs (Fossa *et al.* 2002, Miyazaki & Tagawa 2002, Gauvin *et al.* 2006, Hanton & Rabemampianina 2006), monkeys (Ohmura *et al.* 1999, Horii *et al.* 2002, Hassimoto & Harada 2003, Gauvin *et al.* 2006), pigs (Zhao *et al.* 2001, Kano *et al.* 2005) and rabbits (Eckardt *et al.* 1998, Benardeau *et al.* 2000). Because anaesthetics are known to alter the sensitivity to drugs (Sakaguchi *et al.* 2005, Takahara *et al.* 2005), it is highly desirable to study ECGs in conscious unrestrained animals (Hamlin *et al.* 2003, Provan *et al.* 2005, Shiotani *et al.* 2005). It is essential to assess at an early preclinical stage the potential of new drugs to modify ECG intervals. However, at that stage, drug availability is often limited and an animal with a small body weight (BW) would be preferred. The guineapig can thus be an excellent animal model for measuring QT prolongation. It has specific ion channels similar to humans (Busch *et al.* 1994) and it is more sensitive to cardiac glycosides than rats (Felzen *et al.* 1989). The ECG of guineapigs resembles that of humans with easily identifiable P, Q, R, S and T waves. Their T wave is distinctly separated from the QRS complex. The guineapig is a sensitive model in predicting the QT interval lengthening effects of new drugs in patients

(Shiotani *et al.* 2005, Takahara *et al.* 2006). The guineapig requires a small amount of the test article and its housing is less expensive than that of monkeys or dogs (Lu *et al.* 2001, Zicha *et al.* 2003).

The goal of the present study was to develop a method allowing for continuous recording of BP, heart rate and ECG in conscious, freely moving guineapigs. For this purpose, we have used a previously described telemetry system that is fully implantable (Hess *et al.* 1996, Kramer *et al.* 2000, Kramer & Kinter 2003).

## Materials and methods

### *Animals*

Normotensive male Dunkin Hartley guineapigs weighing between 242 and 611 g were delivered from Harlan, Horst, The Netherlands, group-housed during the acclimatization period (7 days) and pair-housed four days after implantation of the telemetry device, with appropriate environmental enrichment (shelter, hay and straw). Group- or pair-housing is an important need for social species like guineapigs and should be provided wherever possible to improve scientific validity and animal welfare. All animals were maintained under identical conditions and had free access to drinking water and normal pelleted food (no. 3418, Provimi Kliba SA, CH-4303 Kaiseraugst, Switzerland). All animals were housed in climate-controlled conditions with a 12 h light/dark cycle in accordance with the guidelines of the Basel Cantonal Veterinary Office (licence no. 164). To enable the recognition of individuals within the group, each animal was tattooed inside the ear.

### *Surgical procedure*

After the acclimatization period, 19 guineapigs were pretreated with vitamin C (1 g/L, Fluka GmbH, no. 95210, Buchs, Switzerland) in drinking water at least one week before and two weeks after surgery. On the day of implantation of the telemetry device, guineapigs received a subcutaneous injection of the fluoroquinolone antibiotic enrofloxacin (10 mg/kg, Baytril 2.5%, Bayer, Provet AG,

Lyssach, Switzerland). The guineapigs were weighed before surgery and pretreated subcutaneously with tramadol hydrochloride (50 mg/kg, Tramal, Grünenthal, Mitlödi, Switzerland). Anaesthesia was induced and maintained by inhalation of 2.5% isoflurane (70% O<sub>2</sub> + 30% N<sub>2</sub>O). To avoid dry eyes, a drop of Viscotears was put in each eye of the guineapig. Guineapigs were instrumented microsurgically with a telemetry device implanted in the peritoneal cavity under sterile conditions. Bipolar electrodes were implanted to record a lead II Apex-Base ECG (right thoracic ventral serratus muscle – external oblique abdominal muscle). The sensing BP catheter was placed in the descending aorta below the renal arteries, pointing upstream. The catheter was secured in place with a cellulose patch and medical tissue adhesive (Vetbond, no. 1469 SB, 3M, St Paul, MN, USA). Using a non-absorbable suture Ethilon II 4-0 (Ethicon, EH7144, Johnson & Johnson, St Stevens-Woluwe, Belgium), the transmitter was sutured to the inside of the abdominal wall 1 cm underneath the incision muscle layer. The ECG electrodes were fixed with a Prolene 5.0 suture (Ethicon, Noderstedt, Germany). The abdominal musculature was closed with a Vicryl 4-0 suture (Ethicon, V3040, Johnson & Johnson) and the dermis with disposable skin stapler (Precise, DS-15, 3M). After surgery, vitamin C (30 mg/kg subcutaneously, vitamin C Streuli 10%, G Streuli & Co AG, Uznach, Switzerland) and carprofen (3 mg/kg, Rimadyl, Pfizer, distributed by Dr E Gräub AG, Bern, Switzerland) were given to each guineapig. Tramadol hydrochloride (25 mg/kg, Tramal, Grünenthal, Mitlödi, Switzerland) was administered subcutaneously once a day for two days after surgery. Guineapigs that did not withstand microsurgery in good condition were euthanized with carbon dioxide.

#### *Telemetry system and data collection*

Telemetry units were obtained from Data Sciences (St Paul, MN, USA). The implantable transmitter (0.7 mm diameter, 15 cm catheter length, 11 g weight, model

C50-PXT) was designed to measure arterial BP (ABP) and ECG intervals. Implants were gas sterilized and provided pre-calibrated (relative to a vacuum) by the manufacturer. Before implantation of the transmitters, calibration was verified to be accurate within 3 mmHg. The transmitters' signals were coded and monitored by a receiver (RPC-1, Data Sciences). The signal from the receiver was consolidated by a multiplexer (Data Exchange Matrix, Data Sciences) and was sent to a designated personal computer (Dell, Optiplex, GX270, Dublin, Ireland). Arterial pressures (APs) were normalized by using an input from an ambient pressure reference (APR-1, Data Sciences).

BP and ECG data were collected continuously using the Dataquest ART Gold (Data Sciences) acquisition system (version 3.01). BP signals were sampled at 500 Hz. Systolic arterial pressure (SAP), mean arterial pressure (MAP) and diastolic arterial pressure (DAP) were collected at 5 min intervals during 24 h, resulting in a series of 864 data points for each guineapig. Hourly BP means were calculated. ECG signals were sampled at 1000 Hz. ECG waveforms were collected at 5 min intervals during 10 s. RR and QT intervals were analysed using EMKA software (ECG-Auto, version 1.5.8.15, EMKA Technologies, Paris, France). QTc was calculated using Bazett's formula:  $QTc = QT / RR^{1/2}$ , where QT is expressed in milliseconds (ms) and RR in seconds (s). BPs are expressed in millimetres of mercury (mmHg). ECG intervals are expressed in milliseconds (ms).

#### *Experimental design*

The first part of the study was dedicated to the evaluation of post-surgical recovery and to the analysis of BP and ECG signals during the eight weeks following implantation of the telemetry device. In the second part of the study, BP and ECG responses to pharmacological agents were measured 3–20 weeks after telemetry implantation to validate the technique and to evaluate the ability of the telemetry device to transmit changes in ABP and ECG intervals. All haemodynamic and ECG baseline values were the same in each experimental group.

### Reference compounds

Sotalol (Mepha Pharma AG, Aesch, Switzerland – 10, 30 and 100 mg/kg *per os* [p.o.]), dofetilide (Sequoia Research, Oxford, UK – 0.1, 0.3, 1 and 3 mg/kg p.o.), and terfenadine (Sigma-Aldrich, Buchs, Switzerland – 30 and 100 mg/kg p.o.) were used as positive references in this study. Enalapril (Sandoz Pharmaceuticals AG, Cham, Switzerland – 10 mg/kg p.o.) was used as a negative reference. The doses of the reference compounds were calculated based on the doses used in experiments to assess QT prolongation in dogs (Sasaki *et al.* 2005, Shiotani *et al.* 2005, Toyoshima *et al.* 2005). Purified water was used as vehicle. The oral administration volume was 1 mL/kg.

### Statistical analysis

All data are presented as mean  $\pm$  standard error of the mean. Statistical analyses were performed by analysis of variance using Statistica (StatSoft) and the Student–Newman–Keuls procedure for multiple comparisons. The null hypothesis was rejected when  $P < 0.05$ .

## Results

Nineteen guineapigs were instrumented at two different time points. In the first group of 11 guineapigs that underwent surgery, four were euthanized 24 h after surgery

due to thrombus formation in the aorta (lameness of the rear legs). In the second group of eight animals, two guineapigs were euthanized immediately after surgery for the same reason. All other guineapigs were in normal condition throughout the whole study period.

Six guineapigs were monitored for BW, ABP and ECG measurements during the eight weeks following the implantation of the telemetry system. Once a week, a 24 h average was obtained for all experimental variables. After implantation of the radio-transmitters, the animals recovered rapidly as shown by their BWs and ABPs.

Before implantation of the telemetry device, the baseline value of BW was  $376 \pm 36$  g. During the first week, BW was measured every day and the BW losses ranged between 3 and 13%. BW gain returned to normal after two weeks. Eight weeks after the implantation, BW had increased significantly by  $58 \pm 3\%$  compared with baseline values ( $P < 0.001$ , Table 1).

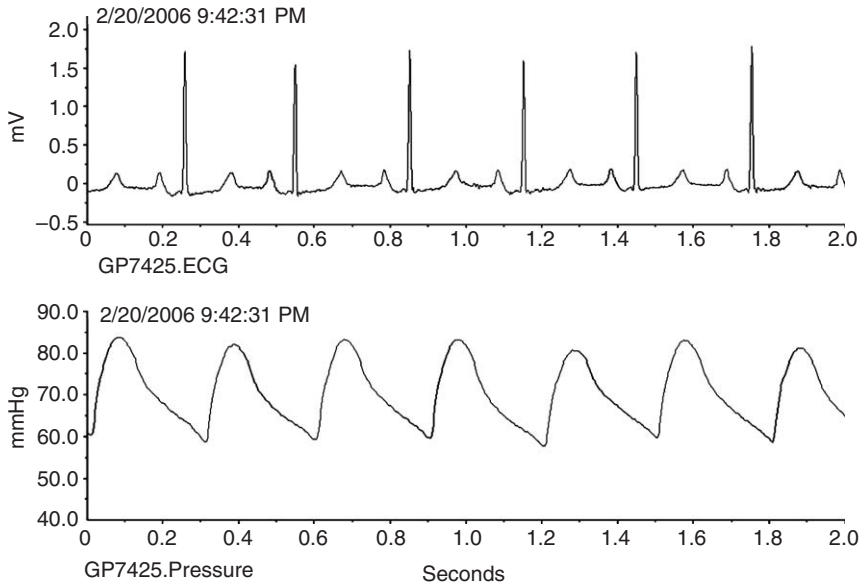
As shown in Table 1, BP reached stable values from week 3 onwards. During the first two weeks after surgery, mean ABP was  $68 \pm 2$  mmHg; it then decreased by 7% and was stable until the end of the experiment. The six-week average values (from weeks 3–8) for SAP, MAP and DAP were  $72 \pm 2$ ,  $63 \pm 2$  and  $55 \pm 2$  mmHg, respectively. The pulse pressure signal (SAP minus DAP) was  $17.0 \pm 0.3$  mmHg. There was no clear

**Table 1** Body weight (BW), arterial blood pressure and electrocardiographic intervals over eight weeks after implantation of the telemetry device in untreated guineapigs

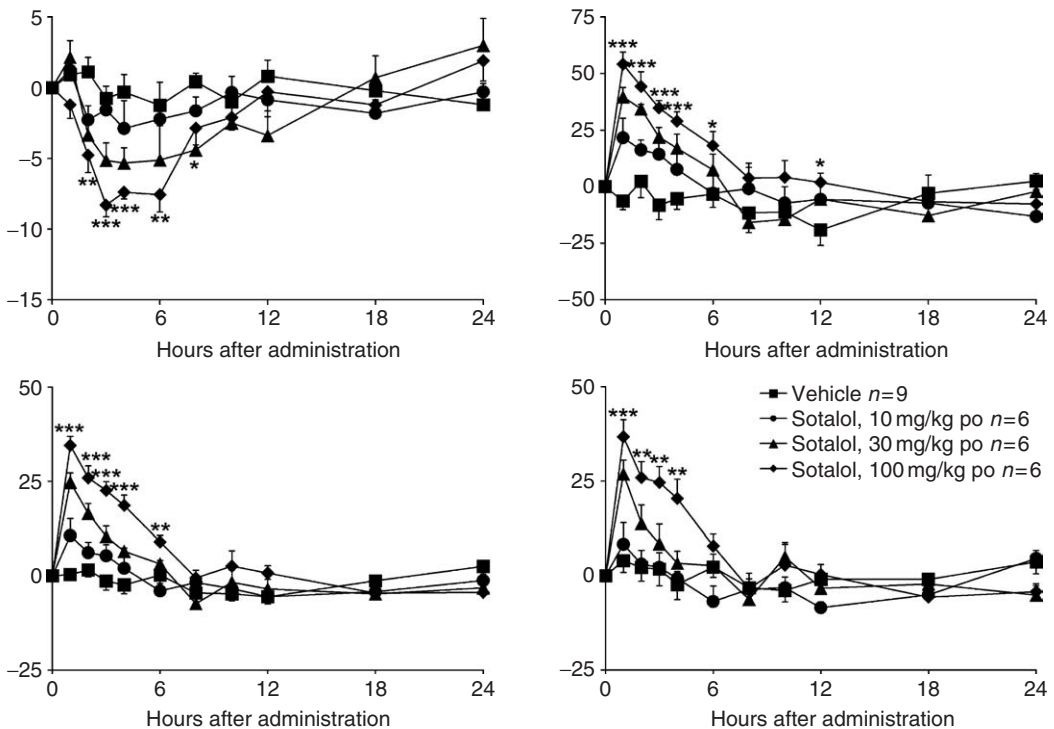
Time (week)	BW (g)	SAP (mmHg)	MAP (mmHg)	DAP (mmHg)	PR (ms)	QRS (ms)	QT (ms)	RR (ms)	QTc (ms)
0	$376 \pm 36$	–	–	–	–	–	–	–	–
1	$364 \pm 36$	$77 \pm 2$	$68 \pm 1$	$59 \pm 1$	$66 \pm 2$	$18 \pm 1$	$121 \pm 3$	$219 \pm 8$	$258 \pm 6$
2	$394 \pm 39$	$77 \pm 2$	$68 \pm 2$	$58 \pm 2$	$62 \pm 2$	$17 \pm 1$	$114 \pm 2$	$209 \pm 8$	$251 \pm 7$
3	$416 \pm 48$	$72 \pm 2$	$64 \pm 2$	$55 \pm 2$	$69 \pm 2$	$20 \pm 1$	$127 \pm 3$	$233 \pm 3$	$264 \pm 5$
4	$456 \pm 60$	$71 \pm 3$	$62 \pm 2$	$54 \pm 2$	$64 \pm 3$	$18 \pm 1$	$120 \pm 5$	$218 \pm 7$	$256 \pm 7$
5	$492 \pm 63$	$71 \pm 3$	$63 \pm 2$	$55 \pm 2$	$65 \pm 2$	$18 \pm 2$	$121 \pm 5$	$216 \pm 5$	$260 \pm 9$
6	$528 \pm 61$	$72 \pm 2$	$64 \pm 2$	$55 \pm 2$	$65 \pm 2$	$19 \pm 2$	$118 \pm 6$	$214 \pm 7$	$256 \pm 9$
7	$550 \pm 63$	$71 \pm 1$	$62 \pm 1$	$54 \pm 2$	$67 \pm 2$	$19 \pm 2$	$122 \pm 23$	$224 \pm 9$	$206 \pm 6$
8	$596 \pm 63$	$72 \pm 1$	$63 \pm 2$	$54 \pm 2$	$70 \pm 2$	$18 \pm 1$	$123 \pm 2$	$237 \pm 10$	$254 \pm 5$
Average (3–8 weeks)		$72 \pm 2$	$63 \pm 2$	$55 \pm 2$	$67 \pm 2$	$19 \pm 1$	$122 \pm 4$	$224 \pm 7$	$254 \pm 5$

$n=6$ . All data are presented as mean  $\pm$  standard error of the mean. Each value represents a mean of the 864 data points (see Materials and methods)

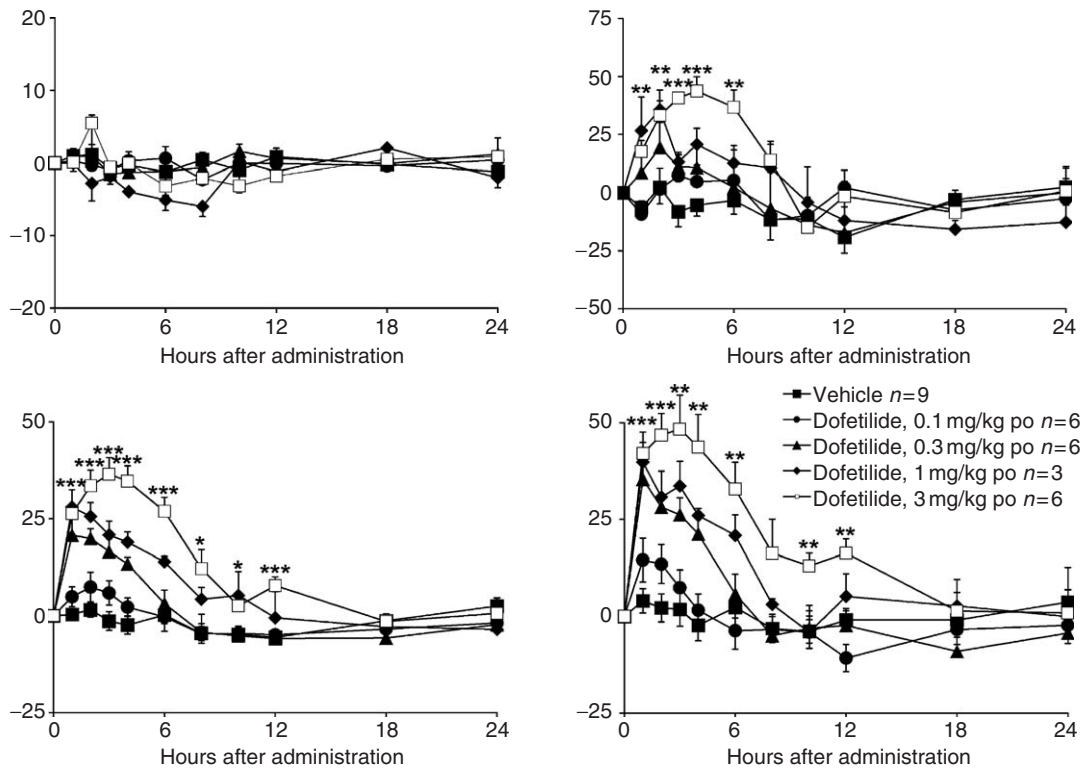
SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure



**Figure 1** Original recordings of arterial blood pressure and electrocardiographic (ECG) intervals in a conscious freely moving guineapig at eight months after implantation of the telemetry transmitter. Traces of telemetry show a lead II Apex-Base ECG and a blood pressure signal over 2 s



**Figure 2** Changes in mean arterial pressure (MAP) and electrocardiographic (ECG) intervals in conscious guineapigs after single doses of sotalol (10, 30 and 100 mg/kg p.o.). All data are presented as mean  $\pm$  standard error of the mean. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$



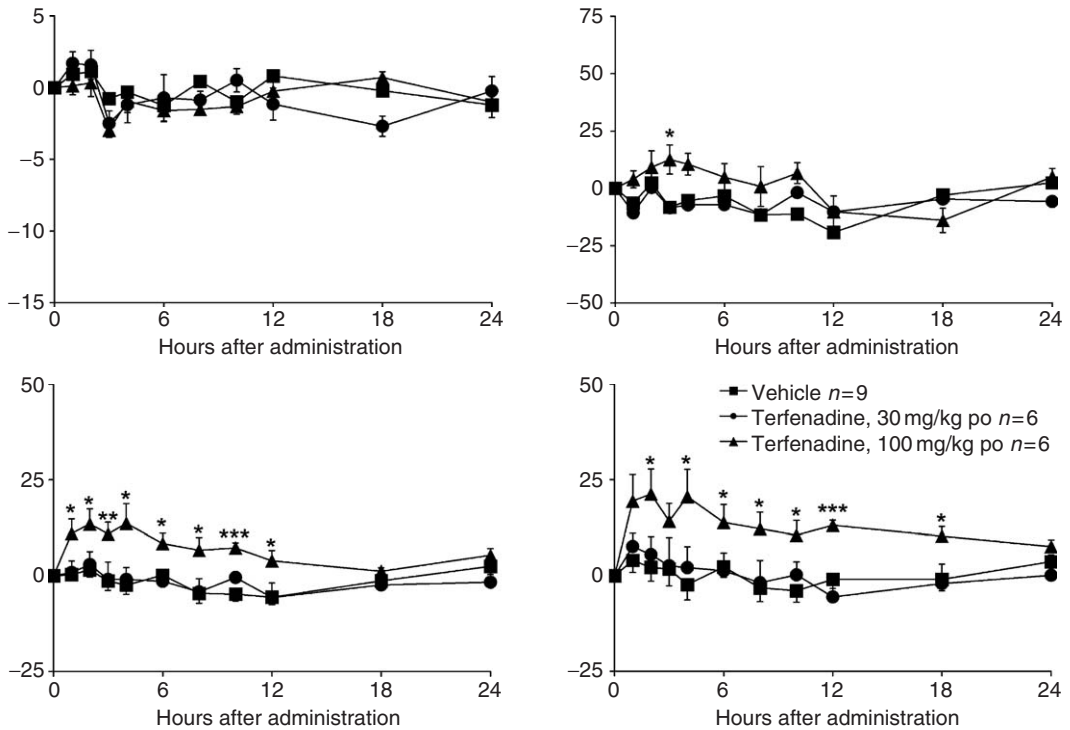
**Figure 3** Changes in mean arterial pressure (MAP) and electrocardiographic (ECG) intervals in conscious guineapigs after single doses of dofetilide (0.1, 0.3, 1 and 3 mg/kg p.o.). All data are presented as mean  $\pm$  standard error of the mean. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$

evidence of circadian rhythms in conscious guineapigs implanted with a telemetry device and no significant differences over time as the animals got older. For ECG intervals, the six-week average values for PR, QRS, QT, RR and QTc intervals were  $67 \pm 2$ ,  $19 \pm 1$ ,  $122 \pm 4$ ,  $224 \pm 7$ , and  $254 \pm 5$  ms, respectively (Table 1). Original recordings of ABP and ECG intervals in a conscious guineapig eight months after implantation of the telemetry device are shown in Figure 1. Both waveforms were similar to those obtained at the beginning of the experiment. The ECG signal showed clearly positive T and P waves eight months after surgery.

Single oral administration of sotalol dose-dependently decreased MAP and increased RR, QT and QTc intervals in freely moving guineapigs compared with vehicle-treated animals. The maximal decreases in MAP were  $2 \pm 1$ ,  $5 \pm 1$  and  $8 \pm 1$  at 10, 30 and

100 mg/kg, respectively (Figure 2). The time to maximal MAP decrease was 3 h and the duration of the effect was 10 h. Uncorrected QT, QTc calculated according to the Bazett's formula, and RR intervals dose-dependently increased after oral administration of sotalol. The maximal increases in QTc were  $8 \pm 6$ ,  $27 \pm 4$  and  $37 \pm 5$  ms at 10, 30 and 100 mg/kg, respectively (Figure 2). The maximal increases in QTc were observed after 1 h and QTc returned to baseline 8 h after administration. No significant changes were observed in PR and QRS intervals (data not shown).

Single oral administration of dofetilide dose-dependently increased RR, QT and QTc intervals in telemetered guineapigs. No significant effect on MAP was observed (Figure 3). The maximal increases in QTc were  $15 \pm 6$ ,  $35 \pm 7$ ,  $40 \pm 8$  and  $48 \pm 9$  ms at 0.1, 0.3, 1 and 3 mg/kg, respectively (Figure 3). Maximal increases in RR, QT



**Figure 4** Changes in mean arterial pressure (MAP) and electrocardiographic (ECG) intervals in conscious guineapigs after single doses of terfenadine (30 and 100 mg/kg p.o.). All data are presented as mean  $\pm$  standard error of the mean. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$

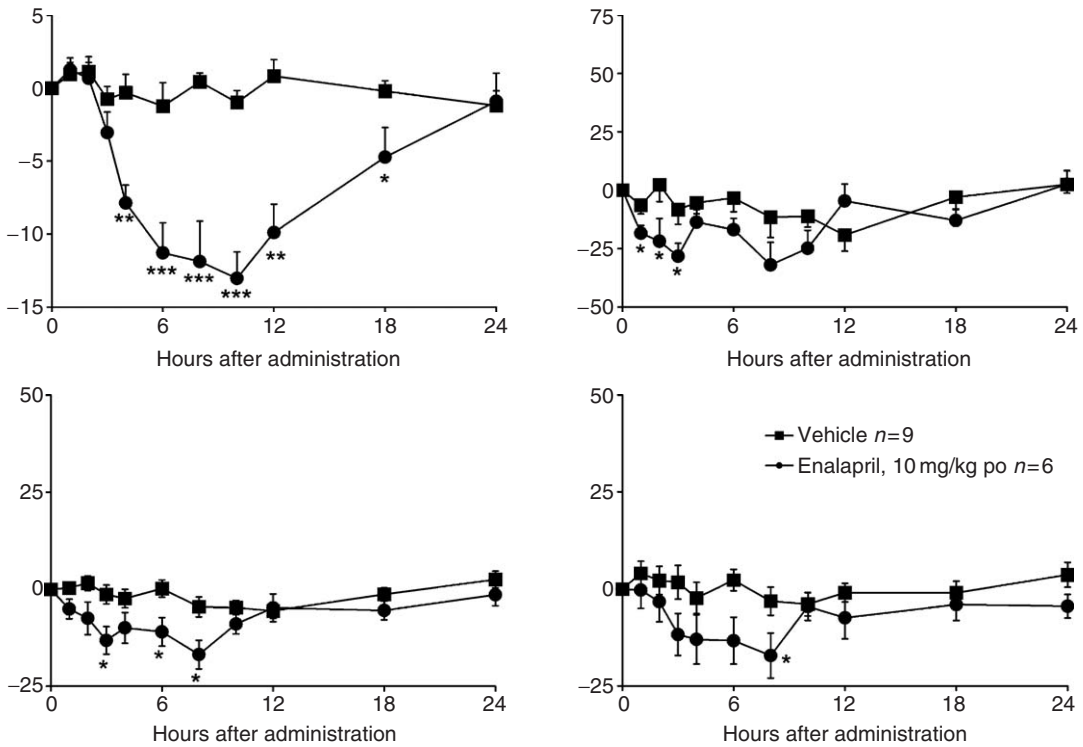
and QTc were observed between 1 and 3 h. The durations of RR, QT and QTc prolongation were 8, 12 and 12 h, respectively. No significant changes were observed in PR and QRS intervals (data not shown).

Terfenadine (100 mg/kg p.o.) had no effect on MAP in telemetered guineapigs. In contrast, 2 h after administration, QTc was increased by  $21 \pm 7$  ms (Figure 4) and the increase was still detectable at 18 h. Similarly, 3 h after administration, RR was increased by  $13 \pm 6$  ms. At 30 mg/kg, no effect was observed, either on MAP or on QTc (Figure 4).

Enalapril decreased QTc by  $17 \pm 6$  ms and RR by  $28 \pm 6$  ms at a dose of 10 mg/kg (Figure 5). ECG returned to normal 12 h after administration. MAP started to decrease significantly 3 h after gavage. The maximal BP decrease was  $13 \pm 2$  mmHg ( $P < 0.001$ ) (Figure 5). MAP returned to baseline 24 h after drug administration.

## Discussion

In the first part of the present study, we show that it is possible to monitor ECG intervals and ABP in conscious freely moving guineapigs by using an intraperitoneal approach for the implantation of the telemetry system. In the first group of 11 guineapigs, 64% survived microsurgery. In the second group of eight, the survival rate increased to 75%. The most important factor influencing the success rate was the use of microsurgery under sterile conditions. No signs of piloerection, poor general conditions, or weight loss were observed in any of the 13 telemetered guineapigs. Chronic implantation of the telemetry device did not lead to anatomic or macroscopic alterations in the abdominal cavity and no inflammation of the peritoneum or infection was observed. In this study, we have refined the telemetry approach used in rats. Guineapigs lack an



**Figure 5** Changes in mean arterial pressure (MAP) and electrocardiographic (ECG) intervals in conscious guineapigs after enalapril 10 mg/kg p.o. All data are presented as mean  $\pm$  standard error of the mean. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$

enzyme that catalyses the conversion of glucose to vitamin C (Cabbabe & Korock 1986, Silverstein & Landsman 1999). They cannot produce their own vitamin C, so that it must be supplied in food or drinking water. The pre- and post-treatment with ascorbic acid is essential to achieve good postoperative care. However, as in the rat, a recovery period of 2–3 weeks is necessary. In our experiments, the telemetric measurements were then stable and the guineapigs resumed normal body weight gain. All 13 guineapigs were monitored until the battery was empty and were used in the validation study for QT prolongation. The maximal experimentation time was eight months (Figure 1).

In the second part of the present study, we show that guineapigs can also be used as an alternative to dog and primate models for the assessment of cardiovascular safety. The guineapig model is often used to measure the

efficacy of antihypertensive agents (Veniant *et al.* 1992, 1994, DePasquale *et al.* 1994). This study shows that ECG intervals can also be measured in conscious guineapigs. QT is known to inversely correlate with heart rate (Hayes *et al.* 1994, Batey & Doe 2002, Hamlin *et al.* 2003). In our study, we used Bazett's formula to correct QT for heart rate. We tested three positive and one negative reference compounds in the guineapig model. After vehicle treatment, the individual hourly means of the QTc intervals varied from 229 to 294 ms. The maximal QTc changes from baseline after administration of the vehicle ranged from  $-3.9 \pm 3.0$  to  $4.0 \pm 3.1$  ms. Therefore, the increase in QTc after drug administration has to be larger than 8–10 ms to suggest drug-induced QT prolongation in conscious guineapigs. In this study, the maximal increases in QTc exceeded this threshold of 8 ms after single oral administration of

sotalol (30 and 100 mg/kg), dofetilide (0.1, 0.3, 1 and 3 mg/kg) and terfenadine (100 mg/kg). These results demonstrate that the guineapig model is suitable for detecting QT prolongations after oral administration of reference compounds. Our results are consistent with previous findings from other laboratories (Hamlin *et al.* 2003, Testai *et al.* 2004, Shiotani *et al.* 2005). Plasma concentrations were not measured in our study but the doses of the three reference compounds were similar to those given orally to other animal species, with similar effects on QTc (Benardeau *et al.* 2000, Fossa *et al.* 2002).

Although large animal species like dogs and primates are often used in cardiovascular safety pharmacology experiments, our study shows that ECG and ABP measurements can be performed in conscious guineapigs by using the intraperitoneal approach for the implantation of the telemetry device. In addition, we show that a small animal species such as the guineapig can be used to assess the potential of these compounds for QT interval prolongation at an early stage in drug development.

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