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Original article

Conscious and anesthetized non-human primate safety pharmacology models: Hemodynamic sensitivity comparison ☆

S. Authier [a,b,*], J.F. Tanguay [c], S. Fournier [a], D. Gauvin [b], M. Legaspi [a,b], F. Chaurand [a], C. Breault [a], E. Troncy [b]

[a] LAB Research Inc., 445 Armand Frappier, Laval, Quebec, Canada H7V 4B3
[b] GREPAQ — Department of veterinary biomedicine, Faculté de médecine vétérinaire, Université de Montréal, P.O. box 5000, St-Hyacinthe, Quebec, Canada J2S 7C6
[c] Research Center, Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec, Canada H1T 1C8

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ABSTRACT

Introduction: Drug-induced cardiovascular effects identified in conscious cynomolgus monkeys equipped with tethers and prepared for radiotelemetry were compared with results from anesthetized non-human primate (cynomolgus and rhesus) models. **Methods:** Remifentanil (4.0 μg/kg, bolus), esmolol (2.0 mg/kg, bolus) and dopamine (0.05 mg/kg/min, 30 min infusion) were given intravenously to all models. **Results:** Remifentanil decreased heart rate (HR), systolic, mean and diastolic systemic arterial pressures (SAP) in anesthetized animals while conscious monkeys presented an increase in HR, systolic, mean and diastolic SAP, as seen in humans for the respective state of consciousness (conscious and anesthetized). Esmolol decreased HR, systolic, mean and diastolic SAP in anesthetized monkeys while only HR, systolic and mean SAP achieved a statistically significant decrease in the conscious model. The amplitude of SAP reduction was greater in anesthetized models, while the amplitude of HR reduction was greater in the conscious and anesthetized cynomolgus models than in the anesthetized rhesus model. Dopamine induced a significant increase in HR, systolic, mean and diastolic SAP in anesthetized models without any statistically significant effect on HR and SAP in the conscious model. **Discussion:** The amplitude of hemodynamic and chronotropic alterations induced by positive control drugs was generally greater in anesthetized than in conscious models and statistical significance was achieved more often with the anesthetized models. These results suggest that an anesthetized model may be valuable as part of a drug screening program for cardiovascular safety evaluations in addition to a conscious model.

1. Introduction

Repolarization-associated ventricular tachyarrhythmia has received considerable attention over the past years from regulatory agencies as highlighted in ICHS7A and ICHS7B guidelines (U.S. Food and Drug Administration, 2001, 2005) and from the scientific community (Detweiler, 1985; Redfern et al., 2003). A variety of methodologies to assess QT interval prolongation and analyze torsadogenic potential have been developed (Fossa, Wisialowski, & Crimin, 2006; Matsunaga et al., 1997; Spence, Soper, Hoe, & Coleman, 1998; Tattersall, Dymond, Hammond, & Valentin, 2006). On the other hand, systemic arterial pressure is recognized as a significant risk factor for mortality at all ages in humans (Kannel, 2000). A meta-analysis in human patients revealed that a 2 mm Hg change in blood pressure translates into a 10% change in stroke and a 7% change in death from ischaemic heart disease (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). These observations highlight the importance of sensitive safety evaluation methodologies in drug development. Non-clinical models used for drug safety assessment have been characterized using several approaches. Recently, statistical power simulations were calculated based on historical hemodynamic, inotropic and chronotropic data from a Beagle dog model (Chiang, Smith, Main, & Sarazan, 2004). Conscious and anesthetized animal models for the identification of torsadogenic effect have been discussed both for small and large laboratory animals (Hamlin, Kijtawornrat, Keene, & Hamlin, 2003; Vormberge, Hoffmann, & Himmel, 2006). On the other hand, there is a paucity of data comparing conscious and anesthetized models for the identification of hemodynamic alterations using positive control drugs. The current study compares hemodynamic and chronotropic responses of conscious and anesthetized non-human primate (NHP) models to positive control drugs. Importantly, the goal was not to confirm the effects of control drugs which have been extensively characterized in animals and humans but to

☆ Experimental work was undertaken at LAB Research Inc., 445 Armand Frappier, Laval, Quebec, Canada H7V4B3.

* Corresponding author. LAB Research Inc., 445 Armand Frappier, Laval, Quebec, Canada H7V 4B3. Tel.: +1 450 973 2240x1403; fax: +1 450 973 2259.
E-mail address: authiers@labresearch.com (S. Authier).

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compare the sensitivity of non-clinical screening models, including their limitations when used in the drug development industry.

2. Methods

2.1. Statement on use and care of animals

During the study, care and use of animals were conducted in accordance with principles outlined in the current Guide to the Care and Use of Experimental Animals published by the Canadian Council on Animal Care and the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). LAB Research Inc.'s facility is AAALAC accredited. All procedures were conducted as per Standard Operating Procedures (SOPs) in place, and according to Good Laboratory Practices (GLP).

2.2. Animal housing and preparation

For conscious evaluations, 4 cynomolgus (*Macaca fascicularis*) monkeys (2 males and 2 females) were surgically prepared with telemetry transmitters (TL11M2-D70-PCT™, DSI, St-Paul, MN, USA) and femoral vein infusion catheters and were equipped with jackets and tethers (Lomir, Notre-Dame-de-l'Île Perrot, QC, CAN) connected to continuous infusion pump (AS50, Baxter, Mississauga, ON, CAN). Analgesic (buprenorphine, Temgesic™, 0.05 mg/kg, Schering-Plough, Welwyn Garden City, Hertfordshire, UK) was administered by intramuscular (IM) injection upon completion of the surgery and every 8 h for at least 24 h post-surgery. Four (4) cynomolgus (*M. fascicularis*) and 4 rhesus (*Macaca mulatta*) monkeys (2 males and 2 females each) were used for anesthetized cardiovascular evaluations. At study initiation, monkeys were 2.7 to 5.8 years old and weighed between 2.5 and 5.9 kg. The animal room environment was controlled (temperature 21 ± 3 °C, humidity 30–70%, 12 h light, 12 h dark, 10–15 air changes per h) and temperature and relative humidity were monitored continuously. A standard certified commercial primate chow (Certified Primate Diet 2055C™, Harlan Teklad, Madison, WI, USA) was available to each monkey twice daily.

2.3. Experimental methods

For unconscious NHP evaluations, anesthesia was induced with isoflurane using a mask, followed by intubation. Animals were placed on a heating pad and inhaled a mixture of oxygen (O_2) and isoflurane (AErrane™, Baxter Corporation, Mississauga, ON, CAN) with the O_2 flow meter and the vaporizer set at 1.0 L/min, and 1.5 to 2.0%, respectively. Respiratory rate was maintained between 10 and 13 breaths/min with an inspiratory airway pressure between 15 and 20 cm H_2O using a mechanical ventilator (2002, Hallowell EMC, Pittsfield, MA, USA). During anesthesia, monitoring included heart rate and pulsatile hemoglobin saturation in O_2 (VetOx 4404™ pulse oximeter, Heska, Fribourg, Switzerland). Anesthetized monkeys were instrumented with a systemic arterial catheter placed in the aorta approximately at the level of the renal artery, a left ventricular catheter inserted through the left carotid, and a Swan–Ganz catheter (Edwards LifeSciences, Irvine, CA, USA) placed in the pulmonary artery under fluoroscopy imaging. Hemodynamic parameters were continuously recorded in anesthetized monkeys, using a computerized data acquisition system (Modular Instruments Inc., Malvern, PA, USA).

Positive control drugs included remifentanil (Ultiva®, Abbott Laboratories Ltd., Vaughan, ON, CAN), esmolol (Brevibloc®, Baxter Corporation, Mississauga, ON, CAN) and dopamine (Inotropin®, Bristol-Myers Squibb, Montreal, QC, CAN). Dose levels and administration protocol were the same for conscious and unconscious NHP models. Dose levels above human clinical doses were selected to induce moderate hemodynamic changes and assess the sensitivity of both models. Conscious animals were freely moving during administration and received control drugs through a permanent femoral catheter. Remifentanil and esmolol were given as an intravenous (IV) bolus at 4.0 μg/kg and 2.0 mg/kg, respectively. Dopamine was administered as a 0.05 mg/kg/min continuous infusion over 30 min.

2.4. Statistical methods

Statistical analysis was carried out using SAS version 9.0 (Cary, NC, USA). The analysis was performed using an analysis of variance (ANOVA) with the treatment and the NHP model for each parameter and the significance of inter-group delta differences was analyzed by Dunnett's *t*-test. Delta effect was calculated as the difference between baseline and peak drug effect post-treatment. The amplitude of drug-induced effects was calculated as percentage of baseline.

3. Results

3.1. Cardiovascular effects induced by remifentanil

Remifentanil induced a statistically significant decrease in systolic, mean and diastolic systemic arterial pressures associated with a reduction in heart rate in anesthetized cynomolgus and rhesus monkeys (as shown in Fig. 1). In contrast, the same drug administered to conscious cynomolgus monkeys induced a slight increase in systolic, mean and diastolic systemic arterial pressures. Changes in heart rate were not statistically significant in the conscious cynomolgus NHP model. Individual data review revealed that all animals presented an increase in heart rate after remifentanil with increases above 40% of baseline in some cases. The elevated response variability most likely contributed to the lack of statistical significance but in the context of drug safety evaluation, these changes would be considered of pharmacological importance. Effects on systolic, mean, and diastolic arterial pressures were significantly more important in anesthetized cynomolgus (between group comparison; $p=0.003$, $p=0.006$, $p=0.005$) and rhesus (between group comparison; $p=0.02$, $p=0.02$, $p=0.008$) monkeys than the changes observed in the conscious cynomolgus NHP model. The effect on heart rate was also more important in anesthetized cynomolgus ($p=0.03$) and rhesus ($p=0.02$) NHP models than in the conscious cynomolgus NHP model. There was no statistically significant difference between the two monkey strains for the anesthetized NHP models for any of the parameter evaluated.

3.2. Cardiovascular effects induced by esmolol

In all anesthetized and conscious NHP models, esmolol induced a reduction in heart rate with a concomitant decrease in systolic, mean and diastolic systemic arterial pressures (Fig. 2). If the decrease observed in the 4 parameters was statistically significant for both anesthetized NHP models, in the conscious cynomolgus model, the decrease was not statistically significant for the diastolic systemic arterial pressure. Pulse pressure was significantly reduced in both anesthetized models, and also in the conscious NHP model. There was significant difference in the amplitude of decrease observed with each model. Again, the effect was significantly more important in anesthetized cynomolgus monkeys for systolic ($p=0.0001$), mean ($p=0.0003$) and diastolic ($p=0.0003$) arterial pressures, when compared to conscious cynomolgus monkeys. The anesthetized rhesus NHP model also presented more important reduction of systolic ($p=0.049$) and mean ($p=0.01$) arterial pressures in comparison to the conscious cynomolgus model. There was no significant difference between the two anesthetized NHP models for hemodynamic effects. The effect on heart rate was significantly more important in conscious ($p=0.04$) and anesthetized ($p=0.02$) cynomolgus monkeys than in anesthetized rhesus monkeys. There was no significant difference between conscious and anesthetized cynomolgus monkeys for heart rate effects.

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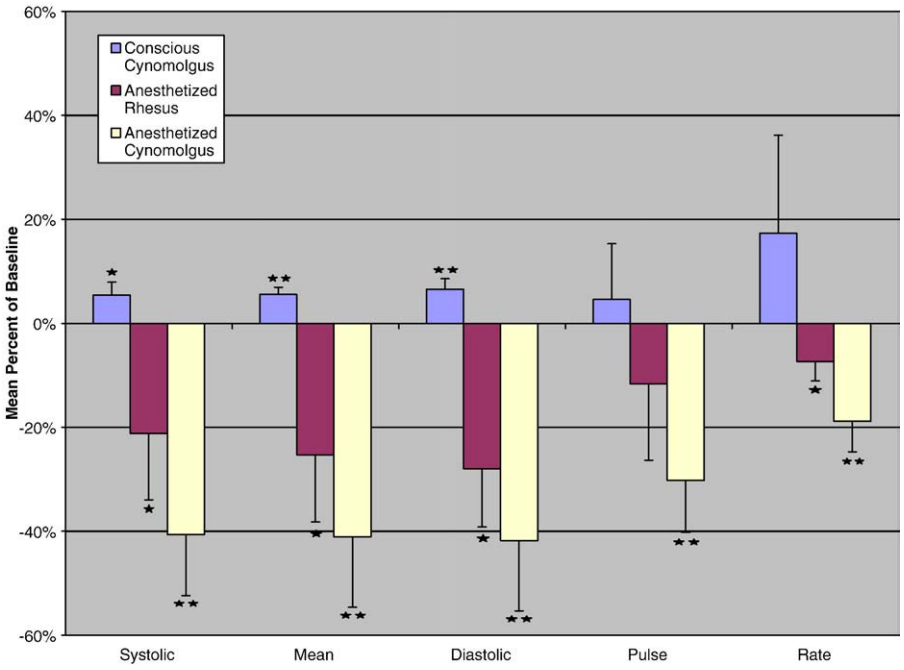

Fig. 1. Maximal cardiovascular effects (systolic, mean, diastolic systemic arterial pressures, arterial pulse pressure and heart rate) of a remifentanil (4.0 μg/kg) intravenous bolus in conscious freely-moving cynomolgus monkeys ($n=4$), anesthetized rhesus monkeys ($n=4$) and anesthetized cynomolgus monkeys ($n=4$). *$p<0.05$ for comparison to baseline. **$p<0.01$ for comparison to baseline. ***$p<0.001$ for comparison to baseline.

3.3. Cardiovascular effects induced by dopamine infusion

Dopamine in anesthetized cynomolgus and rhesus models resulted in significant increases of systolic, mean and diastolic arterial pressures (Fig. 3). In contrast, no statistically significant increase in arterial pressures was noted in the conscious cynomolgus model. Again, individual data review showed that all animals presented an increase in systemic arterial pressure following dopamine reaching up to +23%,

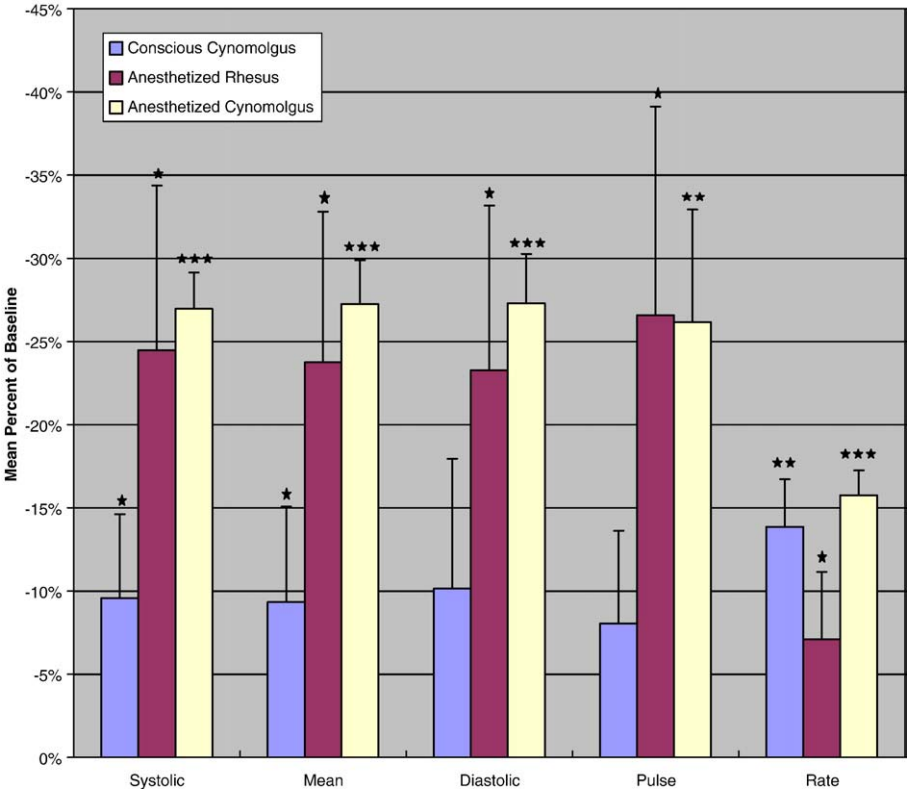

Fig. 2. Maximal cardiovascular effects (systolic, mean, diastolic arterial pressures, arterial pulse pressure and heart rate) of an esmolol (2.0 mg/kg) intravenous bolus in conscious freely-moving cynomolgus monkeys ($n=4$), anesthetized rhesus monkeys ($n=4$) and anesthetized cynomolgus monkeys ($n=4$). *$p<0.05$ for comparison to baseline. **$p<0.01$ for comparison to baseline. ***$p<0.001$ for comparison to baseline.

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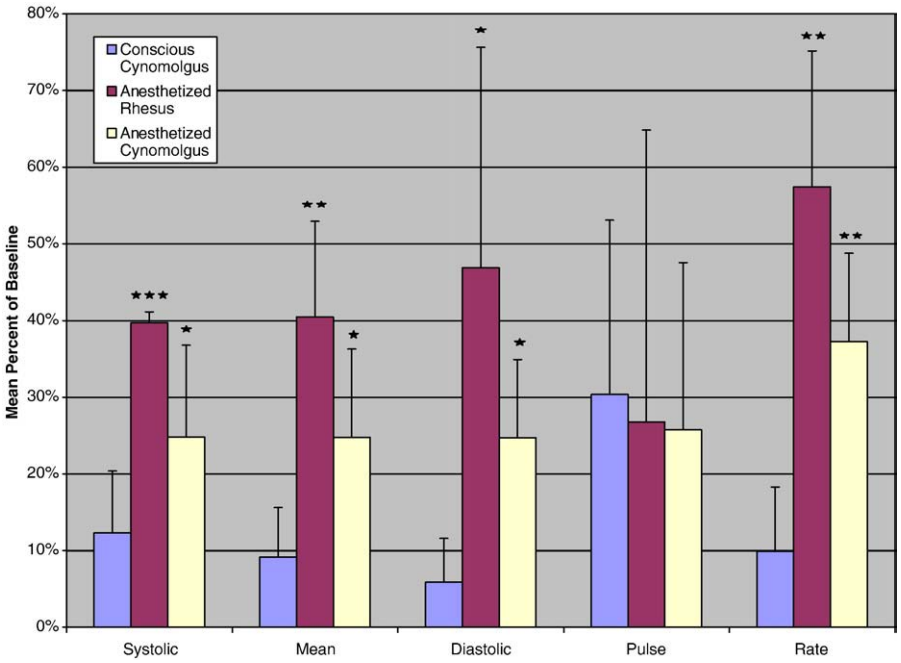

Fig. 3. Maximal cardiovascular effects (systolic, mean, diastolic arterial pressures, arterial pulse pressure and heart rate) of a dopamine (0.05 mg/kg/min) intravenous infusion in conscious freely-moving cynomolgus monkeys ($n=4$) and anesthetized rhesus monkeys ($n=4$) and anesthetized cynomolgus monkeys ($n=4$). *$p<0.05$ for comparison to baseline. **$p<0.01$ for comparison to baseline. ***$p<0.001$ for comparison to baseline.

which was considered pharmacologically significant. The amplitude of diastolic ($p=0.03$) arterial pressure alterations was greater in anesthetized cynomolgus monkeys than in conscious animals. The effect on systolic ($p=0.006$) and mean ($p=0.009$) systemic arterial pressures was more important in the anesthetized rhesus model when compared with the conscious cynomolgus model. No statistically significant chronotropic effect was observed in the conscious cynomolgus model with the power used ($n=4$), while a significantly increased heart rate was noted in both cynomolgus and rhesus anesthetized NHP models (Fig. 3). No difference in amplitude of response was observed for any parameter between both anesthetized NHP models.

4. Discussion

While the number of new drugs and biological applications submitted to the FDA is declining, most investigational products entering clinical trials are unsuccessful, increasing the overall costs of drug development (U.S. Food and Drug Administration, 2004). The need to perform more applied scientific work to develop tools to evaluate safety and effectiveness of new products is essential to improve the critical path from laboratory concept to commercial product.

The current study assessed sensitivity of conscious and anesthetized NHP models for the detection of hemodynamic and chronotropic effects. Cynomolgus monkeys have been widely used for regulatory cardiovascular safety assessments (Gauvin, Tilley, Smith, & Baird, 2006). The extensive use of cynomolgus over rhesus monkeys in conscious cardiovascular models may result from the smaller size of cynomolgus monkeys, reducing costs of test article manufacturing; abundant historical data available at each testing facilities for this strain; milder aggressive behaviours in cynomolgus monkeys (Zumpe & Michael, 2005); as well as sporadic limitations of rhesus monkeys supplies. On the other hand, rhesus monkey offers some advantages for unconscious NHP models due to its larger size, which facilitates heart chamber instrumentation and decreases hemodynamic impacts of intracardiac catheters on heart function (e.g. Swan–Ganz).

Remifentanil is an ultra short-acting (μ)-opioid agonist that has been used in conscious and anesthetized humans. The monkey dose of 4.0 μg/kg is equivalent to 1.3 μg/kg in humans after conversion with the human equivalent dose factor based on body surface area (U.S. Food and Drug Administration, 2002). A dose of remifentanil comparable to the one used in monkeys is reported to induce a transient increase in systolic blood pressure and heart rate when given as a bolus to conscious humans (Glass et al., 1993). In contrast, remifentanil was reported to induce hypotension and bradycardia when administered to anesthetized humans (Elliott et al., 2000). Drug effects obtained with monkeys were representative of the human response for the respective state of consciousness (conscious and anesthetized). These observations reinforce the need to include conscious animal data when using anesthetized animal data to extrapolate to the conscious human response.

Cardiovascular changes following esmolol administration were characteristic of beta$_1$ receptor blocker in both conscious and anesthetized NHP models, with negative chronotropic effects and decreased systemic arterial pressures (Cuneo, Zales, Blahunka, & Benson, 1994; Gorczynski, Murthy, & Hwang, 1984; Kindler, Schumacher, Schneider, & Urwyler, 1996). The amplitude of hemodynamic and chronotropic effects following esmolol administration was suggestive of model specific sensitivity. Once again decrease in systemic arterial pressures was more important in both anesthetized NHP models than in the conscious NHP model, suggesting a greater sensitivity of the anesthetized NHP model. Bradycardia induced by esmolol was more important in cynomologus (both conscious and anesthetized) when compared with rhesus monkeys, while baseline heart rate was similar in both strains for anesthetized animals (cynomolgus 119 bpm ± 4; rhesus 120 bpm ± 16). It remains that expected pharmacological effects were observed with both models and illustrate the variability of different animal strains. Similarly, different animal species such as dogs and monkeys are expected to present pharmacological responses that will differ to a given extent depending on the test article. As a result, using different animal species (e.g. dogs and monkeys) and different states (conscious and anesthetized) in the safety screening program could increase the overall sensitivity and most importantly increase the predictive value to the human response.

Results following dopamine infusion revealed that hemodynamic pressor effects (Abdul-Rasool, Chamberlain, Swan, & Ward, 1987; Setler, Pendleton, & Finlay, 1975) were more important in anesthetized monkeys. In addition, statistical significance for positive chronotropic

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effects was only achieved in anesthetized NHP models. The amplitude of systemic arterial pressure response was also greater in anesthetized monkeys when compared to the conscious NHP model. As previously reported, anesthesia with isoflurane is expected to result in lower mean arterial pressure baseline, when compared with the conscious state (Hom et al., 1999). Consequently, we could hypothesize that a lower arterial pressure baseline may enable greater pressor effects following dopamine infusion. As observed with remifentanil, lower systemic arterial pressure baseline in the anesthetized NHP model did not impair the sensitivity of this model for identification of hypotensive effects. Our results suggest that anesthetized cardiovascular models (NHP or other species as appropriate) may be valuable as part of the screening program in drug development. This screening step is typically conducted at an early stage of drug development in non-GLP studies using a very limited number of animals. In addition, the lack of statistical significance for some expected effects in the conscious model illustrate limitations of statistical analysis which may not completely capture pharmacologically significant changes when using relatively small group size for non-clinical drug screening. Statistical analysis should be combined with individual data evaluation to confirm that all relevant pharmacological effects have been identified.

Evaluation of drug potential for QT prolongation is an important factor in the choice of the most appropriate *in-vivo* safety model(s). Volatile anesthetics have been shown to prolong QT and QTc intervals in animals and humans (Riley, Schmeling, Al-Wathiqui, Kampine, & Warltier, 1988; Schmeling et al., 1991). As a result, the conscious model is normally preferred for electrocardiographic safety evaluations. It would be interesting to compare the sensitivity of conscious and anesthetized NHP models for electrocardiographic alterations, including use of different anesthesia protocol (isoflurane, sevoflurane, etomidate, alpha-chloralose, propofol, etc.).

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