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# Pharmacokinetics of intravenously and orally administered sotalol hydrochloride in horses and effects on surface electrocardiogram and left ventricular systolic function

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ABSTRACT

Arrhythmias are common in horses. Some, such as frequent atrial or ventricular premature beats, may require long-term anti-arrhythmic therapy. In humans and small animals, sotalol hydrochloride (STL) is often used for chronic oral anti-arrhythmic therapy. STL prolongs repolarization and the effective refractory period in all cardiac tissues. No information on STL pharmacokinetics or pharmacodynamics in horses is available and the aim of this study was to evaluate the pharmacokinetics of intravenously (IV) and orally (PO) administered STL and the effects on surface electrocardiogram and left ventricular systolic function. Six healthy horses were given 1 mg STL/kg bodyweight either IV or PO. Blood samples to determine plasma STL concentrations were taken before and at several time points after STL administration. Electrocardiography and echocardiography were performed at different time points before and after IV STL administration.

Mean peak plasma concentrations after IV and PO administration of STL were 1624 ng/mL and 317 ng/mL, respectively. The oral bioavailability was intermediate (48%) with maximal absorption after 0.94 h, a moderate distribution and a mean elimination half-life of 15.24 h. After IV administration, there was a significant increase in QT interval, but no significant changes in other electrocardiographic and echocardiographic parameters. Transient transpiration was observed after IV administration, but no adverse effects were noted after a single oral dose of 1 mg/kg STL in any of the horses. It was concluded that STL has an intermediate oral bioavailability in the horse and might be useful in the treatment of equine arrhythmias.

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## Introduction

In horses, supraventricular and ventricular arrhythmias can be associated with a wide range of cardiac and non-cardiac diseases. Frequent ventricular premature beats carry a risk of ventricular tachyarrhythmia and even ventricular fibrillation and sometimes requires long-term, anti-arrhythmic therapy (Reef et al., 2014). A high number of atrial premature beats may require treatment as atrial premature beats increase the risk of atrial fibrillation developing (Reef and Marr, 2010; Reef et al., 2014). In the first few days to weeks after cardioversion of atrial fibrillation, reverse remodeling takes place. During this remodeling phase, suppression of atrial premature beats may be important in reducing recurrence rates (van Loon, 2001; Decloedt et al., 2013; De Clercq et al., 2014).

In human medicine, long-term oral anti-arrhythmic treatment is often prescribed to reduce the chances to relapse into atrial fibrillation (Fetsch et al., 2004; Lafuente-Lafuente et al., 2007). Sotalol (STL), a potent, non-cardioselective β-adrenergic blocking agent with class III anti-arrhythmic action, has been shown to have an efficacy equivalent to propafenone and quinidine in preventing atrial fibrillation recurrence, but is significantly better tolerated by human patients (Juul-Moller et al., 1990; Reimold et al., 1993; Derakhchan et al., 2001). In dogs, STL is used to prevent recurrence of atrial flutter and atrial fibrillation (Feld et al., 1986; Li et al., 2008). Unlike many other anti-arrhythmics, STL has a good oral bioavailability (F) (90%) in humans, no major interaction with other drugs, no metabolism and is solely cleared through the urine (Anderson and Prystowsky, 1999). The most important side effects of STL are related to its β-blocking actions and the risk of torsades de pointes (a form of polymorphic ventricular tachycardia). Most anti-arrhythmic drugs currently used in horses have a low F, are difficult for long-term administration or are very expensive. The present study investigates

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the pharmacokinetics of STL in horses and its effect on the surface electrocardiogram (ECG) and left ventricular systolic function.

## Materials and methods

### *Study design*

Six healthy Standardbred horses, with a mean ± standard deviation (SD) age, bodyweight (BW) and height at the withers of 17 ± 3 years, 527 ± 46 kg and 156 ± 23 cm, respectively, belonging to the teaching herd of the Faculty of Veterinary Medicine, Ghent University, were used. The experimental protocol was approved by the Ethical Committee of the Faculty of Veterinary Medicine at Ghent University (case number EC 2012/149, date of approval 23 November 2012).

The horses received STL at an intravenous (IV) and oral (PO) dose of 1 mg/kg BW in a two-way cross-over design, with a wash-out period of 40 days. For the IV study, horses received 1 mg/kg STL (Sotalol Carino, Carinopharm) as a constant rate infusion over a period of 10 min. For the PO administration, after being withheld from feed for 12 h, horses received 1 mg/kg of crushed STL tablets (Sotalol Sandoz) in 2 L of tap water by means of nasogastric intubation.

Blood was withdrawn in heparinized polyethylene tubes just before and at 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 480, 600 and 720 min after administration, and every 12 h after that, until 72 h after administration. Blood samples were immediately centrifuged for 10 min at 4000 *g* and plasma was frozen at –18 °C until drug assay. Clinical signs, heart rate (HR) and respiratory rates were recorded just before each blood sampling. The horses receiving IV STL were under continuous ECG surveillance until 12 h after drug administration. Echocardiography was performed before, and at 60 and 180 min after STL administration.

### *Plasma analysis*

Quantitation of STL in the plasma samples was performed using a liquid chromatographic (LC) tandem mass spectrometric (MS/MS) method, developed and validated in house. To 250 µL of plasma, 25 µL of the internal standard (IS) working solution (1 µg/mL, atenolol) were added and the sample was vortex mixed for 15 s. Subsequently, the sample clean-up consisted of a protein precipitation step using 750 µL of acetonitrile. After a vortex mixing (15 s) and centrifugation step (10 min, 7800 *g*), the supernatant was evaporated to dryness using a nitrogen stream (40 °C). The dry residue was re-dissolved in 250 µL ultra-performance liquid chromatography (UPLC)-grade water by vortex mixing (15 s) and filtered using a syringe filter (Millex-GN, Merck). The filtrate was transferred to an autosampler vial and a 5 µL aliquot was injected onto the LC-MS/MS system.

The LC system consisted of an UPLC Acquity Binary Solvent Manager and Sample Manager with temperature controlled tray and column oven (Waters). Chromatographic separation was achieved on an Acquity UPLC BEH C18 column in combination with an Acquity BEH C18 Vanguard pre-column (Waters). The mobile phases used consisted of 20 mM ammonium formate in UPLC-grade water (A) and UPLC-grade acetonitrile (B). A gradient elution was performed (0–2 min: 97% A, 2–5 min: linear gradient to 20% A, 5–6 min: 20% A, 6–6.5 min: linear gradient to 97% A, 6.5–10 min: 97% A) at a flow-rate of 0.3 mL/min. The LC column effluent was interfaced to a Quattro Premier XE triple quadrupole mass spectrometer with an electrospray ionization source operating in the positive mode (Waters). Instrument parameters were optimized for both analytes (STL and IS) and the following multiple reaction monitoring transitions were selected: STL: mass to charge ratio (m/z) = 273.01 > 255.01 (quantifier ion) and 212.96 (qualifier ion); IS: m/z = 267.06 > 144.96.

The method was validated in house by a set of parameters that were in compliance with the recommendations as defined by the European Community,[1] international guidelines[2] and in literature (Knecht and Stork, 1974). The following parameters were evaluated: linearity (2–2000 ng/mL), within-run and between-run accuracy and precision, limit of quantification (LOQ, 2 ng/mL), limit of detection (LOD 0.26 ng/mL), specificity and carry-over. The validation protocol and the acceptance criteria used were previously described by De Baere et al. (2011).

### *Pharmacokinetic analysis*

Two-compartmental pharmacokinetic analysis was performed with dedicated software (WinNonlin 6.3 Pharsight). The most important pharmacokinetic parameters were calculated: maximal plasma concentration ($C_{max}$), plasma concentration at time 0 ($C_0$), time to maximal plasma concentration ($T_{max}$), area under the plasma concentration-time curve from time 0 to infinite ($AUC_{0-inf}$), absorption rate constant ($k_a$), absorption half-life ($T_{1/2a}$), distribution rate constant ($k_{el\alpha}$), distribution half-life ($T_{1/2el\alpha}$), elimination rate constant ($k_{el\beta}$), elimination half-life ($T_{1/2el\beta}$), clearance (Cl), volume of distribution in the central (Vc) and peripheral (Vp) compartment. The F was calculated for each horse according to the formula:

$$F(\%) = AUC_{0-inf\ PO} / AUC_{0-inf\ IV} \times 100$$

where Cl, Vc and Vp after oral administration were calculated by multiplying the output generated by the modeling software, namely Cl/F, Vc/F and Vp/F, with the F for each individual horse.

Based on the data derived from the single PO administration study, plasma concentrations were predicted for multiple dosing of STL: 1, 2 and 3 mg/kg twice daily for 4 days. Maximal and minimal plasma concentrations at steady state ($Cp_{ss\ max}$ and $Cp_{ss\ min}$) were derived from the dosing interval between 72 h and 84 h. The average plasma concentration at steady state ($Cp_{ss\ av}$) was calculated as follows:

$$Cp_{ss\ av} = AUC_{72h-t} / \tau$$

with t the next time point of administration, 84 h, and τ the dose interval, 12 h.

### *Electrocardiography*

An ECG was recorded using a Televet100 recording system (Engel Engineering Services). A modified base apex configuration as described by Verheyen et al. (2010) was used. The ECG recordings were analysed offline (Televet100 software version 5.0, Engel Engineering Services) by a blinded observer. The duration of the QRS complex and the P wave, and the RR, PQ and QT intervals were measured for 20 cycles before and at 15, 30, 60, 120, 180 and 360 min after STL administration. All values were also corrected using the Fridericia correction (corrected interval = interval/$RR^{(1/3)}$).

### *Echocardiography*

All horses were examined with a HR < 45 beats/min, using an ultrasound unit (GE Vivid 7 Dimension, GE Healthcare) with phased-array transducer (3S, GE Healthcare). A base-apex ECG was recorded simultaneously. All examinations were recorded digitally and analysed offline (EchoPAC software version BT12, GE Healthcare) by a blinded observer. Echocardiographic recordings and measurements were obtained as described elsewhere (Long et al., 1992; Blissitt and Bonagura, 1995). In brief, systolic function was assessed by calculating fractional shortening from left ventricular internal diameter at end-diastole (LVIDd) and end-systole (LVIDs) (FS = ((LVIDd – LVIDs) × 100)/LVIDd) on a right parasternal short axis view M-mode at the chordal level. From a right parasternal left ventricular outflow tract view M-mode of the aortic valve, left ventricular pre-ejection period (LVPEP) was measured from the onset of the QRS complex to the opening of the aortic valve and left ventricular ejection time (LVET) from the opening to closure of the aortic valve. Pre-ejection period to ejection time ratio (LVPEP/LVET) was calculated to reduce the influence of HR on systolic time intervals. For each cycle the instantaneous HR was recorded. Three consecutive cycles were measured to calculate a mean value at each time point (0, 60 and 180 min) for each horse.

### *Statistical analysis*

Statistical analysis was performed using dedicated software (SPSS 21 for Windows, IBM). Pharmacokinetic parameters are reported as mean values ± SD. Linear mixed models with post hoc Dunnett's comparison with baseline values were used to assess the relationship between ECG measurements and between echocardiographic measurements at different time points before and after the administration of STL. Differences were considered statistically significant when $P < 0.05$.

## Results

### *Pharmacokinetics*

Pharmacokinetic variables and plasma concentrations of STL after IV and PO administration are summarized in Table 1 and Fig. 1, respectively. In Fig. 2, the predicted steady state concentrations at a dose of 1, 2 and 3 mg/kg PO twice daily in fasted horses are shown. Table 2 summarizes the predicted AUC, $Cp_{ss\ av}$, $Cp_{ss\ max}$ and $Cp_{ss\ min}$.

### *Electrocardiography*

Electrocardiographic variables at baseline and at different time points after IV STL administration are summarized in Table 3. Compared to baseline, mean QT interval was significantly increased at 15 (mean increase ± SD: 35 ± 27 ms, 6.0%, $P = 0.026$), 30 (37 ± 24 ms, 6.2%, $P = 0.018$) and 60 (35 ± 25 ms, 5.6%, $P = 0.039$) min after STL administration. No significant difference was found for the corrected QT interval (QTc), although QTc at 15 min after STL

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[2] February 2011. Guidance for Industry, Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food producing animals: validation of analytical methods used in residue depletion studies. In: VICH GL 49 (2012-Final).

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