Determination of Oral Dosage and Pharmacokinetic Analysis of Flecainide in Horses

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ABSTRACT. To determine oral dosage and to evaluate the pharmacokinetics in horses of orally administered flecainide, an antiarrhythmic drug, the correlations between its plasma concentration and PR, QRS and QT intervals in equine electrocardiograms (ECG) were investigated. Six healthy horses were administered a randomly ordered dose of 4 or 6 mg/kg of flecainide acetate. The ECG was monitored (heart rate (HR), PR, QRS, and QT intervals) and blood was taken at timed intervals to measure the plasma flecainide concentrations pre- and post-administration. The maximum plasma concentration reached 1014 ± 285 (SD) ng/ml in 45 ± 13 min and 1301 ± 400 ng/ml in 60 ± 37 min for doses of 4 and 6 mg/kg flecainide, respectively. From the pharmacokinetic analysis, clearance rates were 14.6 ± 6.4 and 11.7 ± 5.2 ml/kg/min and terminal elimination half-lives were 228 ± 53 and 304 ± 87 min. The QRS and QT intervals increased significantly for both doses following administration, though HR and PR intervals did not change. Plasma flecainide concentrations were significantly correlated with QRS (r=0.935, P<0.001) and QT intervals (r=0.753, P<0.001). In conclusion, plasma concentrations of flecainide for treating equine atrial fibrillation were obtained by oral administration of 4 and 6 mg/kg, and the drug was rapidly eliminated from plasma in horses.

KEY WORDS: equine, flecainide, oral administration, pharmacokinetics.

Flecainide is an antiarrhythmic agent of class Ic of Vaughan-Williams' classification [6]. It slows intracardiac conduction and prolongs the refractory period to a lesser extent [4]. In humans, flecainide has been shown to be effective in treating both supraventricular and ventricular arrhythmias. It is particularly effective as a drug for converting paroxysmal atrial fibrillation to sinus rhythm [5, 7, 10, 11]. We have shown in a previous study that flecainide given intravenously is a safe and effective agent for treating equine atrial fibrillation [8]. For the conversion of atrial fibrillation to sinus rhythm, a total dose of 1.4 ± 0.63 mg/kg flecainide was required intravenously, the time to conversion was 7.0 ± 3.15 min and the effective plasma concentration was 1,303 ± 566 ng/ml [8]. However, that is the only report on the use of flecainide for treating atrial fibrillation in horses, thus, nothing is known about its behavior following oral administration or its pharmacokinetics in horses. The purpose of this study was to determine the oral dosage and pharmacokinetics of flecainide required to achieve the clinically effective plasma concentration determined in our previous study.

MATERIALS AND METHODS

Horses and dosage: Six healthy horses (four Thoroughbreds and two Anglo Arabs; three males, two females and one gelding; average age 4.8 ± 1.6 yr, and average weight 448 ± 30 kg) were used. Food was withheld from each horse for 12 hr before oral administration of flecainide. Teflon catheters (14-gauge) were inserted into the left jugular vein after local anesthesia was administered. A randomly ordered dose of 4 or 6 mg/kg of flecainide acetate (Eisai, Tokyo) in 2 l water was administered by nasogastric tube, with an interval of at least one week between each oral administration as a washout period.

Experimental protocol: The electrocardiograms (ECG) were recorded by base-apex lead at pre-administration and 1, 4, 8 and 24 hr after administration using a Holter-type electrocardiograph (SM-50; FUKUDA DENSHI Co., Ltd., Tokyo). Heart rate (HR) and PR, QRS, and QT intervals were measured by computer using an ECG analysis system (Softron Co., Ltd., Tokyo). Blood was drawn from the jugular venous catheter pre-administration and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr after administration. Blood samples were placed into heparinized tubes and centrifuged at 3,000 rpm for 10 min immediately after being drawn. The plasma concentration of flecainide was assayed using high-performance liquid chromatography [9].

Pharmacokinetic analysis: Plasma flecainide concentrations for each horse were examined by noncompartmental analysis using WinNonlin™ Professional v. 1.5 (Pharsight Corp., Mountain View, CA, U.S.A.). The elimination rate constant (λ1) was calculated on the basis of the last 3 data points. Areas under the plasma concentration versus time curves (AUC) and areas under the first moment curves (AUMC) were calculated according to the trapezoidal rule, and last detected in plasma samples (C last) to infinity were estimated as C last/λ1. The volumes of distribution at steady state (Vss) were calculated by the equation Vss = dose/(AUMC)/(AUC)². Body clearance (Cl) was calculated by the equation Cl = dose/AUC. Terminal elimination half-lives (T1/2) were calculated by the equation T1/2=0.693/λ1. The maximum plasma concentrations (Cmax) and times to achieve Cmax (Tmax) were determined by visual inspection.
of the individual plasma concentration versus time curves.

Statistical analysis: All data are expressed as mean ± SD. Heart rate and PR, QRS, and QT intervals were standardized for each horse for each dose with respect to its pre-administration value, which was defined as 100%, and were compared using repeated-measures ANOVA with Student-Newman-Keuls’ multiple-range test (P<0.05). Correlations of standardized PR, QRS, and QT intervals with plasma flecainide concentrations were analyzed by calculating the Pearson product-moment correlation coefficient. (P<0.05).

RESULTS

Plasma flecainide concentration rapidly increased after oral administration, reached a peak within 1 hr, then decreased and had completely disappeared by 24 hr after administration (Fig. 1). The Cmax reached 1014 ± 285 ng/ml in 45 ± 13 min and 1301 ± 400 ng/ml in 60 ± 37 min following oral administration of 4 and 6 mg/kg doses of flecainide, respectively. The results of the pharmacokinetic analysis are listed in Table 1.

Table 2 shows the HR and PR, QRS, and QT intervals obtained by ECG over time following the administration of flecainide. Heart rate and PR interval did not change significantly for either dose following administration. The QRS and QT intervals elongated significantly 1 hr after administration of 4 mg/kg of flecainide. The QRS intervals were significantly prolonged at 1 and 4 hr after administration of 6 mg/kg of flecainide, although the QT intervals did not change significantly.

Table 3. Changes in heart rate (HR), PR, QRS and QT intervals after oral flecainide administration

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Table 1. Pharmacokinetic variables of flecainide in horses after oral administration</th>
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<tbody>
<tr>
<td>Variable</td>
<td>4</td>
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<tr>
<td>Cmax (ng/ml)</td>
<td>1,014 ± 285</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>45 ± 13</td>
</tr>
<tr>
<td>Vss (ml/kg)</td>
<td>4,795 ± 1,620</td>
</tr>
<tr>
<td>CI (ml/kg/min)</td>
<td>14.6 ± 6.4</td>
</tr>
<tr>
<td>T₁/₂ (min)</td>
<td>228 ± 53</td>
</tr>
<tr>
<td>AUC (ng•hr/ml)</td>
<td>5,117 ± 1,511</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. Cmax=Maximum plasma concentration. Tmax=Time to achieve maximum plasma concentration. Vss=Steady state volume of distribution. CI=Body clearance. T₁/₂=Terminal elimination half-life. AUC=Area under the plasma concentration versus time curve.
DISCUSSION

Flecainide has not previously been reported to have been administered orally in horses, and an effective clinical dosage has not been determined. In this study, we compared two oral dosages with reference to plasma concentrations that have been shown to be clinically effective via oral or intravenous administration in humans, and via intravenous application in horses. In our previous study, we administered flecainide intravenously to horses with atrial fibrillation and converted all tested horses to sinus rhythm with a total dose of 1.4 ± 0.63 mg/kg administered over a period of 7.0 ± 3.15 min [8]. The effective plasma flecainide concentration required for conversion to sinus rhythm was 1303 ± 566 (range 460 to 1908) ng/ml. In this study, Cmax (4 mg/kg dose: 1014 ± 285 (range 571 to 1406) ng/ml; 6 mg/kg dose: 1301 ± 400 (range 917 to 2032) ng/ml) with oral administration were similar to the effective plasma concentration with intravenous administration. With oral administration, the plasma concentration remained near the effective value between 0.5 hr and 2–4 hr following administration of the two dosages (Fig. 1). These results suggest that plasma flecainide concentration for the cardioversion of atrial fibrillation can be attained by oral administration of either 4 or 6 mg/kg flecainide.

The two major metabolites of flecainide acetate are meta-0-dealkylated flecainide and meta-0-dealkylated lactam of flecainide. Because these possess little or no detectable antiarrhythmic activity, the pharmacological action depends on unchanged flecainide concentrations [2]. Therefore, it is thought that the pharmacokinetics of the unchanged flecainide is the clinically important variable.

In humans, Tmax with oral administration is 1.5 to 2.5 hr and T1/2 is approx 11 hr [1]. In the present study, Tmax in horses was shorter than in humans, being 45 ± 13 and 60 ± 37 min after oral administration for the 4 and 6 mg/kg doses, respectively. Half-life was also shorter in horses than in humans. Therefore, flecainide had almost completely disappeared from the plasma 24 hr after administration of both dosages in horses. The reason for these differences may be that Vss in horses is less than in humans, although Cl is similar in both species.

The QRS and QT intervals following the 4 mg/kg dose and the QRS intervals following the 6 mg/kg dose elongated significantly at 1 and 4 hr post-administration (Table 2). The magnitudes of prolongation of the QRS and QT intervals were similar to those of the horses previously administered 2.0 mg/kg of flecainide intravenously, a safe dose. Plasma concentrations of flecainide in horses in this study were similar to the therapeutic concentration in our previous study. In neither of these studies did horses show any abnormal clinical signs following flecainide administration, suggesting these were clinically efficacious but safe doses.

In humans, the indications are that prolongation of the PR and QRS intervals correlate with the antiarrhythmic action of the drug [3]. We have shown that increases in QRS and QT intervals were associated with plasma flecainide concentrations, although PR intervals did not elongate in either study in horses as they do in humans [8]. These results suggest that the QRS and QT intervals more accurately reflect the effect of flecainide on the cardiac muscle in horses.

In conclusion, plasma concentrations of flecainide equivalent to those previously shown to be clinically effective in treating paroxysmal atrial fibrillation in horses were achieved with oral administration of 4 and 6 mg/kg of flecainide and were maintained for several hours. Pharmacokinetic analysis indicated that flecainide is rapidly eliminated from plasma in horses. Plasma flecainide
concentrations were significantly correlated with the length of the QRS and QT intervals.

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REFERENCES