Evaluation of the pharmacokinetics and bioavailability of intravenously and orally administered amiodarone in horses

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Objective—To determine the clinical effects and pharmacokinetics of amiodarone after single doses of 5 mg/kg administered orally or intravenously.

Animals—6 healthy adult horses.

Procedure—In a cross-over study, clinical signs and electrocardiographic variables were monitored and plasma and urine samples were collected. A liquid chromatography-mass spectrometry method was used to determine the percentage of protein binding and to measure plasma and urine concentrations of amiodarone and the active metabolite desethylamiodarone.

Results—No adverse clinical signs were observed. After IV administration, median terminal elimination half-lives of amiodarone and desethylamiodarone were 51.1 and 75.3 hours, respectively. Clearance was 0.35 L/kg•h, and the apparent volume of distribution for amiodarone was 31.1 L/kg. The peak plasma desethylamiodarone concentration of 0.08 µg/mL was attained 2.7 hours after IV administration. Neither parent drug nor metabolite was detected in urine, and protein binding of amiodarone was 96%. After oral administration of amiodarone, absorption of amiodarone was slow and variable; bioavailability ranged from 6.0% to 33.7%. The peak plasma amiodarone concentration of 0.14 µg/mL was attained 7.0 hours after oral administration and the peak plasma desethylamiodarone concentration of 0.03 µg/mL was attained 8.0 hours after administration. Median elimination half-lives of amiodarone and desethylamiodarone were 24.1 and 58.6 hours, respectively.

Conclusion and Clinical Relevance—Results indicate that the pharmacokinetic distribution of amiodarone is multicompartamental. This information is useful for determining treatment regimens for horses with arrhythmias. Amiodarone has low bioavailability after oral administration, does not undergo renal excretion, and is highly protein-bound in horses.

Amiodarone is a benzofuran-derived drug that was developed more than 35 years ago for management of myocardial ischemia in humans. Although the antiarrhythmic and preventative effects of amiodarone on atrial flutter and AF have been known since the early 1980s, the drug has been used most extensively for treatment of ventricular arrhythmias. Because of its potency as an antiarrhythmic drug, amiodarone is receiving renewed attention for potential use in treatment and prevention of AF.

Amiodarone has high lipid solubility and is taken up extensively by tissues, resulting in a high volume of distribution and prolonged elimination t1/2. Estimates of elimination t1/2 vary, depending on study design and sensitivity of the analytic methods used. A model for estimating pharmacokinetic variables of amiodarone in ponies has been described. As is true in humans, AF is one of the most common cardiac arrhythmias in horses. The chief clinical sign in horses is exercise intolerance. The prognosis for return to normal sinus rhythm is influenced by the duration for which the arrhythmia has persisted and by atrial diameter; duration of the arrhythmia for longer than 6 months or development of the arrhythmia in association with atrial dilatation is associated with a poor prognosis for successful cardioversion. Atrial dilatation can be caused by mitral valve regurgitation and can also result from AF. In many horses with AF, no underlying cardiac disease is detected and treatment is often successful. After cardioversion, horses generally return to the previous level of athletic ability.

The standard treatment for AF is administration of QS, although up to 76% of treated horses develop 1 or more adverse effects, including urticaria, nasal mucosal edema, colic, diarrhea, laminitis, tachycardia, anaphylactic shock, syncope, or sudden death. In some countries, QS has become difficult to obtain and will likely become more expensive. These factors have stimulated the search for an alternative and less toxic drug for treatment of chronic AF in horses.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>t1/2</td>
<td>Half-life</td>
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<tr>
<td>QS</td>
<td>Quinidine sulfate</td>
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<tr>
<td>LOQ</td>
<td>Limit of quantification</td>
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<tr>
<td>LOD</td>
<td>Limit of detection</td>
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<tr>
<td>AUC0–inf</td>
<td>Area under the curve to infinity</td>
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<tr>
<td>CI</td>
<td>Clearance</td>
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<tr>
<td>Vd</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>t1/2el</td>
<td>Terminal elimination t1/2</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>Tmax</td>
<td>Time to maximum plasma concentration</td>
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</table>
Multiple antiarrhythmic drugs are used for treatment of AF in humans, some of which have already been investigated for use in horses. Intravenously administered flecainide (a class IC antiarrhythmia drug) and amiodarone (a class III antiarrhythmia drug) have been used for treatment of horses with AF. The use of flecainide in horses appeared promising for treatment of acute AF in a study, but it was not useful in horses with chronic AF because of elicitation of ventricular dysrhythmias. In another study, of 6 horses were converted to sinus rhythm after administration of amiodarone. In that study, horses received 5 mg of amiodarone/kg per hour for 1 hour followed by 0.83 mg/kg/h for 23 hours and 1.9 mg/kg/h for 30 hours. Infusion was discontinued when conversion was achieved or when adverse effects were observed. Because amiodarone appeared to be potentially useful for treatment of chronic AF in horses, the present study was undertaken to investigate the pharmacokinetics of orally and IV administered amiodarone in horses.

Materials and Methods

Study design—In a crossover format, the first phase of the study involved IV administration of a single dose (5 mg/kg) of amiodarone to 3 healthy Standardbred mares with mean ± SD age, body weight, and height at the withers of 9.8 ± 3.5 years, 491.7 ± 19.8 kg, and 156.3 ± 8.9 cm, respectively, that had not been withheld from feed. Horses received the dose of amiodarone as a bolus in the right jugular vein over a period of 2 minutes. Three other horses received an orally administered dose (5 mg/kg) of crushed tablets by means of nasogastric intubation after being withheld from feed for 12 hours. Four hours after receiving the oral treatment, horses were given hay ad libitum. Blood was withdrawn from the left jugular vein in heparinized polyethylene tubes just before drug administration; 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, and 480, and 720 minutes after administration; and every 12 hours after that until 7 days after administration. Blood samples were centrifuged at 3,000 X g immediately after collection to obtain plasma. In 3 horses that received amiodarone IV, total urine samples were collected 0, 1, 2, 3, 4, 6, 8, and 12 hours after treatment. Plasma and urine samples were frozen and stored at −18°C until drug assay. Clinical signs, respiratory rate, and an ECG were recorded at each blood sampling time until 6 hours after drug administration. Information collected from ECG included heart rate, PR interval, QRS wave duration, and QT interval. Immediately before and 7 days after drug administration, complete hematologic and biochemical blood analyses were performed.

In the second phase of the study, which was initiated 60 days after the first phase, the same sampling protocol was followed. Horses that had received amiodarone IV in the first phase were treated orally and vice versa. The experimental protocol was approved by the Ethics Committee of the Faculty Veterinary Medicine at Ghent University.

Plasma and urine analyses—Amiodarone and desethylamiodarone concentrations were measured by use of a validated high-performance liquid chromatography method and tandem mass spectrometry. In brief, 100 µL of a solution of the internal standard tamoxifen (concentration, 10 µg/mL) was added to a 1,000-µL aliquot of plasma or urine. After mixing for 15 seconds, 25 µL of glacial acetic acid was added to deproteinize the mixture and the tube was centrifuged at 9,500 X g for 10 minutes. Thereafter, solid-phase extraction and clean up were performed by use of strong-cation–exchange cartridges that had been previously conditioned with 1 mL of methanol solution and 1 mL of water. After application of the supernatant, cartridges were sequentially washed with 1 mL of 0.1M hydrochloric acid and 1 mL of methanol. Analytes were eluted with 2 mL of a methylene chloride-isopropanol-ammonia solution (78/20/2 [vol/vol/vol]). The elution liquid was evaporated at 40°C under a gentle nitrogen stream. The dry residue was dissolved in 250 µL of 0.1% formic acid in a water-methanol solution (20/80 [vol/vol]). A 100-µL aliquot of that mixture was injected onto the liquid chromatography system combined with an ion-trap mass spectrometer operating in the electrospray positive-ionization mode. For chromatographic separation, a C18 column (5 µm; 100 X 2.1 mm internal diameter) with a guard column of the same type (5 µm; 10 X 2.1 mm internal diameter) were used. An isocratic run of 5 minutes was performed with a mobile phase of acetonitrile (A) and 0.1% formic acid in water (B; ratio, 80A:20B [vol/vol]) at a flow rate of 0.2 mL/min. Quantification was performed by use of ion transitions with mass-over-charge ratios of 646.1 > 572.8 for amiodarone and 618.2 > 546.8 for desethylamiodarone.

The analytic method was validated for linearity, within- and between-day trueness and precision, LOQ, and LOD according to the European Community guidelines for analytic methods. Calibration curves were prepared by adding amiodarone or desethylamiodarone to pooled blank plasma and urine samples at concentrations of 0.005, 0.010, 0.025, 0.050, 0.100, 0.500, 1.000, and 0 µg/mL. The trueness (ie, recovery or the difference between the mean detected and fortified concentrations) and within-day precision of the method were determined by use of 6 blank samples to which known quantities of drug were added at 0.010 and 0.050 µg/mL for plasma and 0.025 and 0.500 µg/mL for urine. The trueness for amiodarone in plasma was −23.9% and –10.7% for the 0.010 and 0.050 µg/mL samples, respectively, and for desethylamiodarone, values of 7.5% and –1.6% were obtained for the 0.025 and 0.500 µg/mL samples, respectively. For urine samples, values were 1.0% and –0.8% for amiodarone and –12.3% and –0.6% for desethylamiodarone at concentrations of 0.025 and 0.500 µg/mL, respectively. All values were within the acceptance range of −30% to +10% for concentrations ≤ 0.010 µg/mL and −20% to 10% for concentrations > 0.010 µg/mL. The precision also fell within the maximum relative SD values of 21.3%, 18.6%, 11.8%, and 16.7% for concentrations of 0.010, 0.025, 0.050, and 0.500 µg/mL, respectively. The between-day trueness and precision were determined by use of samples of plasma with a drug concentration of 0.010 µg/mL and were used for quality control during analyses of the collected samples. Those values were in the specified maximum ranges. The LOQs for plasma and urine were established by analyzing 6 blank samples to which amiodarone and desethylamiodarone (concentration, 0.005 µg/mL) had been added. The LOD was calculated by means of the criterion of a signal-to-noise ratio of 3:1. This corresponded to LODs of 0.0001 and 0.00004 µg/mL, respectively, for amiodarone and desethylamiodarone in plasma and of 0.00016 and 0.00009 µg/mL, respectively, in urine.

Protein binding was determined in plasma samples (n = 6) to which drug had been added at a concentration of 2 µg/mL and allowed to equilibrate for 30 minutes at 37°C. One milliliter of that solution was centrifuged at 9,500 X g for 10 minutes through a filter of 30,000 molecular-weight cutoff. The filtrate was analyzed similarly to plasma samples.

Pharmacokinetic data analysis—The plasma concentration-time curves for data obtained after IV administration of amiodarone in each horse were fitted by use of a
nonlinear least-squares regression-fitting program. The model was determined for best fit on the basis of a smaller value for the Akaike information criterion. The plasma concentration-time curves for those data best fit the 3-compartmental model. The following equation was used to describe the concentration-time curves: 

\[ C(t) = A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t} \]

where \( C(t) \) is the plasma concentration; \( A, B, \) and \( C \) are zero-time intercepts; \( \alpha, \beta, \) and \( \gamma \) are hybrid constants dependent on first-order rate constants. Values for AUC0–inf, Cl, apparent Vd, and t1/2el were calculated according to standard pharmacokinetic equations.

For amiodarone data obtained after oral administration and desethylamiodarone data obtained after IV and oral administration (of amiodarone), noncompartmental methods were used because standard fitting procedures resulted in poor correlations. The AUC0–inf value was calculated via the trapezoidal method. The variables Cmax and Tmax were observed directly from the plasma concentration time plots. Absolute bioavailability (F) was calculated from the following equation:

\[ F = \frac{AUC_{\text{oral}}}{AUC_{\text{IV}}} \times 100 \]

Statistical analysis—Pharmacokinetic variables were reported as median values except for t1/2el, for which a harmonic mean was calculated. Respiratory rate, heart rate, P-R interval, QRS duration, and Q-T interval over time were analyzed by use of single-factor ANOVA. The mean measured values were compared with values obtained before treatment. For all comparisons, values of \( P < 0.05 \) were considered significant.

Results
Administration of amiodarone via IV and oral routes was tolerated well by all horses. Values for hematologic and serum biochemical variables remained within reference ranges for the first (ie, immediately before administration) and second (ie, 7 days after administration) blood samples. Numeric and graphic descriptions of data for respiratory rate, heart rate, PR interval, QRS duration, and QT interval indicated that the condition of equality of variances was satisfied. Results of single-factor ANOVA did not reveal significant differences between mean values for the variables. Although increased heart rate was observed after IV administration of amiodarone, the change was not significant.

Pharmacokinetic variables for amiodarone and desethylamiodarone were given as median and range values and summarized (Tables 1 and 2). Mean ± SD plasma concentrations of amiodarone and desethylamiodarone after IV and oral administration were plotted (Figures 1 and 2). In horses in the IV administration group, plasma concentrations of amiodarone and desethylamiodarone were quantifiable from 5 and 15 minutes, respectively, after administration until 168 hours after administration. In the oral administration group, amiodarone and desethylamiodarone concentrations were quantified in plasma from 30 and 90 minutes, respectively, after administration until 96 and 120 hours after administration. After IV administration, plasma concentrations of amiodarone decreased rapidly in the first phase of the 3-compartment model. The second phase was characterized by a slower decline in concentration and was followed by a very slow decline in concentration in the third phase. In 2 horses, there was a small increase (50 and 100 \( \mu \)g/mL) in plasma amiodarone concentration at 8 and 12 hours, respectively, after administration. In the oral administration group, amiodarone and desethylamiodarone concentrations were quantified in plasma from 5 and 15 minutes, respectively, after administration until 168 hours after administration. Protein binding of amiodarone as analyzed at 2 \( \mu \)g/mL was 96%. No amiodarone or desethylamiodarone could be detected in the urine samples collected until 12 hours after IV administration.

### Table 1—Median and range values of pharmacokinetic variables after a single IV or orally administered dose (5 mg/kg) of amiodarone in 6 healthy horses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (g/mL)</td>
<td>NA</td>
<td>0.14 (0.04–0.17)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.5 (0.7–8.0)</td>
<td>7.0 (3.0–12.0)</td>
</tr>
<tr>
<td>AUC (g•h/mL)</td>
<td>14.5 (11.0–19.6)</td>
<td>2.5 (1.2–5.1)</td>
</tr>
<tr>
<td>Cl (L/kg•h)</td>
<td>0.35 (0.27–0.45)</td>
<td>NA</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>31.1 (14.9–64.5)</td>
<td>NA</td>
</tr>
<tr>
<td>t1/2el (h)</td>
<td>51.1 (38.2–84.0)</td>
<td>24.1 (18.7–36.1)</td>
</tr>
<tr>
<td>F (%)</td>
<td>NA</td>
<td>15.4 (6.0–33.7)</td>
</tr>
</tbody>
</table>

*Harmonic mean.

F = Absolute bioavailability. NA = Not applicable.

### Table 2—Median and range values of pharmacokinetic variables for desethylamiodarone after a single IV or orally administered dose (5 mg/kg) of amiodarone in the same 6 horses as in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (g/mL)</td>
<td>0.08 (0.05–0.11)</td>
<td>0.03 (0.02–0.06)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.5 (0.7–8.0)</td>
<td>8.0 (6.0–14.0)</td>
</tr>
<tr>
<td>AUC (g•h/mL)</td>
<td>7.3 (4.2–10.3)</td>
<td>2.1 (1.2–6.7)</td>
</tr>
<tr>
<td>t1/2el (h)</td>
<td>75.3* (53.8–127.1)</td>
<td>58.6* (48.0–100.8)</td>
</tr>
</tbody>
</table>

* Harmonic mean.
Discussion

The dose (5 mg/kg) of amiodarone used in the present study was chosen on the basis of doses described in pharmacokinetic studies in other species. In this study, there were no changes in respiratory rate, P-R interval, QRS duration, or QT interval and no arrhythmias developed after the single IV dose of amiodarone, findings that corroborated with those from a study in humans. Substantial prolongation of the QT interval without torsades de pointes, however, has been described after administration of several doses of amiodarone in humans and dogs, and has also been reported after a single IV dose in ponies. Horses in the present study had a moderate increase in heart rate after IV administration of amiodarone, a finding that has also been reported in ponies and humans; in contrast, a decrease in heart rate after a single dose of amiodarone has been reported in dogs. The higher heart rate may be explained by the development of hypotension after IV administration.

Pharmacokinetic variables reported for amiodarone vary. This is likely a result of the length of time during which samples were collected in the experiments and the sensitivity of the assays. In the present study, bolus-dose administration and sampling times of 7 days were used to determine bioavailability and calculate standard 2-stage compartmental pharmacokinetic variables. The method of analysis was a liquid chromatography–tandem mass spectrometry method performed on an ion-trap mass spectrometer. These methods yielded an LOQ of 0.005 µg/mL in the plasma and urine samples. Other investigators obtained lower LOQ values by use of either another tandem mass spectrometer system with a more sensitive triple-quadrupole instrument or techniques involving the use of radiolabeled amiodarone. With the latter methods, the terminal elimination phase can be better characterized and a better estimate of elimination t1/2 can be obtained. In 1 study in humans, investigators described a terminal elimination phase of 100 days and an elimination t1/2 of 58 days after a single dose of amiodarone, findings that were in accordance with values reported after long-term administration or use of radiolabeled drug. A drawback in methods involving the use of radiolabeled drug is that it is not always possible to differentiate between parent drug and metabolites. Comparison of pharmacokinetic variables should, therefore, be performed with data collected under the same circumstances, including similar sampling times and sensitivity of analytic methods.

The concentration-versus-time curves for data obtained after IV administration were fitted to a 3-compartment model. Values for mean Vd (31.1 L/kg), Cl (0.35 L/kg•h), and t1/2 (38 to 84 hours) were calculated. Compared with our value, a much longer t1/2 of 16.3 days was calculated in ponies treated with amiodarone by another group. This difference may be explained because a physiologically based pharmacokinetic model was used to estimate pharmacokinetic parameters in that study.

As has been reported in studies in humans, the plasma concentration–time curves in our horses after oral administration did not have good fit for the curve on the basis of compartmental modelling. A delay (0.5 hours) in the appearance of amiodarone in plasma was observed in our horses. In humans, mean lag times of 0.3 to 1.4 hours have been reported, whereas in our horses, mean lag times of 7.0 hours after administration in our horses, whereas mean ± SD values of 7.3 ± 2.9 hours, 5.2 ± 0.6 hours, and 4.8 ± 1.5 hours have been reported in humans. A lower median Cmax (0.14 µg/mL) was observed in our horses, compared with values of 0.5 µg/mL, 1.7 µg/mL, and 0.37 ± 0.22 µg/mL reported in humans. Median bioavailability in the nonfed horses (19.4%) was < 50%, a value that has been reported in dogs and rats, whereas in humans, values of 22% to 86% have been reported. The large variability in absorption observed in the present study was in agreement with findings from pharmacokinetic studies in humans. Such low and variable bioavailability may be attributed to incomplete absorption of the drug and first-pass metabolism in the intestine or liver. Concurrent ingestion of food has a positive influence on bioavailability of amiodarone in humans; investigators in that study concluded that amiodarone has dissolution–rate-
limited absorption and the effects of food and bile result in the improved bioavailability. Whether food intake also increases bioavailability of orally administered amiodarone in horses remains to be investigated.

A secondary peak in plasma concentration 8 to 12 hours after IV administration was observed in 2 horses and may have been a result of enterohepatic cycling. The fact that the highest bioavailability for amiodarone was observed in those 2 horses supports this theory.

Plasma concentrations of desethylamiodarone were measured simultaneously in each sample. This metabolite is important because it has pharmacologic potency and toxicity equal to the parent drug. After administration of the drug in our study, median maximum desethylamiodarone concentrations were 80 and 29 µg/L after IV and oral administration, respectively. The t1/2 of desethylamiodarone was longer than the t1/2 of amiodarone, a finding that was in accordance with data in humans. In an earlier study in which amiodarone was given as an IV infusion, plasma desethylamiodarone concentrations remained low and did not exceed 360 µg/L, a fraction of the amiodarone concentration. This observation has also been made in rats. These findings are different from those reported in a study in which chronic amiodarone administration in humans yielded plasma desethylamiodarone concentrations nearly equal to amiodarone concentrations. This may indicate that there is a species-dependent difference in metabolism, with N-dealkylation being a less important metabolic pathway in horses than in humans. However, long-term administration studies should be performed, with analysis of plasma and liver tissue for amiodarone and desethylamiodarone concentrations, and in vitro experiments with microsomes obtained from equine liver tissue could be performed to confirm this hypothesis.

We observed 96% protein binding for amiodarone in the in vitro ultrafiltration experiments. The protein binding was investigated at 2 µg/mL, since that concentration appears to be a pharmacologically important plasma concentration. Some investigators have questioned the reliability of the ultrafiltration technique for quantification of amiodarone protein binding because of adherence of drug molecules to the filtration devices, but those experiments were conducted with radiolabeled amiodarone; other researchers reported no interference when using analytic-grade amiodarone. The high protein binding we observed was in agreement with findings in other species.

No amiodarone or desethylamiodarone was detected in urine of horses during the 12 hours following IV administration. Because glucuronide conjugates have been detected in urine of treated humans, urine samples in the present study were combined with sodium hydroxide to deglucuronidate the samples, but neither amiodarone nor desethylamiodarone was detected. Similar results have been described in humans and rats. In a study involving rats, little unchanged amiodarone or desethylamiodarone was eliminated in feces or urine. In that study, 94% and 1.7% of a dose of radiolabeled drug was eliminated in feces and urine, respectively, primarily as other nonspecified radioactive metabolites formed from amiodarone and desethylamiodarone. This finding is in contrast to those predicted by the mathematical model used in an earlier study, in which 96% of amiodarone was eliminated as desethylamiodarone in the urine of ponies. These results indicate that metabolism of amiodarone into other compounds is the primary form of elimination. The metabolic fates of amiodarone and desethylamiodarone are unclear. The metabolism of amiodarone and desethylamiodarone in several species, including humans, rats, and rabbits, has been reviewed. Amiodarone is dealkylated to desethylamiodarone in the liver and intestine, primarily in hepatic microsomes. A hydroxylation step in the metabolism of amiodarone has been proposed. Desethylamiodarone may be hydroxylated, dealkylated, and deaminated. Involvement of cytochrome P450 enzymes and species-dependent metabolic steps have been proposed. Deiodination of amiodarone has also been observed, 1 result of which is excretion of free iodide in the urine.

The toxicity of amiodarone has long been known. In the early 1980s, physicians were reluctant to prescribe amiodarone because of adverse effects associated with chronic administration. The uncommon pharmacokinetic features of amiodarone and desethylamiodarone (ie, slow filling of the third compartment of the 3-compartment model and a gradual increase in plasma concentrations toward steady state) are partly responsible for the reluctance to administer amiodarone. In our study, no clinically important adverse effects or changes in results of serum biochemical analyses were observed. Acute adverse effects associated with IV administration of amiodarone are rare. Hypotension is the most common reaction and develops as a result of the vasodilatory and negative inotropic effects of amiodarone. The vasodilatory effect is caused by the solvent (polysorbate 80) in which the drug is suspended and can be managed with dose reduction or routine pressure-supportive measures. Development of acute hepatotoxicity after IV administration of amiodarone has been reported in humans.

Adverse effects associated with chronic (eg, months to years) administration of amiodarone are more frequent and involve the lungs, liver, heart, thyroid gland, gastrointestinal tract, eyes, skin, nerves, and, rarely, the epididymis. Gastrointestinal adverse effects in humans include nausea, anorexia, and constipation. Neurologic adverse effects include ataxia, paresthesia, and development of tremors. In general, clinical signs of toxicity are dose-related and disappear after withdrawal of treatment. Guidelines for treating adverse reactions have been described.

The purpose of the present study was to determine the pharmacokinetics of amiodarone in horses to facilitate development of treatment protocols for horses with acute-onset or chronic AF. An oral treatment protocol could be developed, but associated disadvantages include drug bioavailability that is low and variable among individuals and the long delay between initiation of treatment and onset of suppression of the arrhythmia. Therefore, several weeks may be required to achieve steady-state plasma concentrations and drug costs may be prohibitive. Moreover, failure of long-
term amiodarone treatment (65 mg/kg, q 24 h for 30 days) to resolve AF has been reported in 2 horses.\(^6\)

Amiodarone may be more useful if administered according to a continuous IV infusion protocol. This method of administration has the advantage of rapid filling of the deep compartments and possibly a more rapid onset of action that could lead to cardioversion. Disadvantages associated with this treatment method are that the treatment must be administered in a clinical setting and that, depending on the dose, a higher risk of adverse effects may exist. One protocol for IV infusion of amiodarone has been published; mild signs of hind limb weakness and weight shifting were reported.\(^2\) A serial IV dosing schedule, as was proposed by 1 group of investigators,\(^3\) would be easier to implement in practice, but no clinical data from horses treated via this protocol have been published. Another possibility would be a treatment protocol combining IV and oral dosing, in which the IV dose could be administered in a clinical setting and plasma drug concentrations could be measured. Use of such a protocol would potentially permit slower increases in plasma drug concentrations toward the desired steady-state concentration with fewer adverse effects but would have the disadvantage of increased treatment costs.

Results of the present study confirm that the pharmacokinetics of amiodarone and desethylamiodarone in horses are multicompartmental. The drug is poorly bioavailable after oral administration, does not undergo renal excretion, and is highly protein-bound, similar to findings in other species. However, further pharmacokinetic and pharmacodynamic studies are needed to develop a safe treatment protocol for amiodarone in horses. Studies of long-term dosing and clinical effects and use of more sensitive analytic techniques are needed before amiodarone can feasibly be administered to horses with chronic AF.

References


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