Pharmacokinetics of fenbendazole following intravenous and oral administration to pigs

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Objective—To determine pharmacokinetics and metabolic patterns of fenbendazole after IV and oral administration to pigs.

Animals—Four mixed-breed female pigs weighing 32 to 45 kg.

Procedure—Fenbendazole was administered IV at a dose of 1 mg/kg. One week later, it was administered orally at a dose of 5 mg/kg. Blood samples were collected for up to 72 hours after administration, and plasma concentrations of fenbendazole, oxfendazole, and fenbendazole sulfone were determined by use of high-pressure liquid chromatography. Plasma pharmacokinetics were determined by use of noncompartmental methods.

Results—Body clearance of fenbendazole after IV administration was 1.36 L/h/kg, volume of distribution at steady state was 3.35 L/kg, and mean residence time was 2.63 hours. After oral administration, peak plasma concentration of fenbendazole was 0.07 µg/mL, time to peak plasma concentration was 3.75 hours, and mean residence time was 15.15 hours. Bioavailability of fenbendazole was 27.1%. Oxfendazole was the major plasma metabolite, accounting for two-thirds of the total area under the plasma concentration versus time curve after IV and oral administration. Fenbendazole accounted for 8.4% of the total AUC after IV administration and 4.5% after oral administration.

Conclusions and Clinical Relevance—Results indicate that fenbendazole was rapidly eliminated from plasma of pigs. The drug was rapidly absorbed after oral administration, but systemic bioavailability was low.

Fenbendazole is a thiosubstituted benzimidazole that is widely used in veterinary medicine. The drug is efficacious against important gastrointestinal nematodes of domestic animals. It is extensively metabolized by microsomal oxidation in the liver, and a sequential oxidative pathway for fenbendazole is predominant in most species. Important metabolites of fenbendazole in plasma are oxfendazole and fenbendazole sulfone. In recent years, an extensive knowledge of the pharmacokinetics and metabolism of benzimidazoles in nonruminants has been performed. Plasma concentrations of fenbendazole, oxfendazole, and fenbendazole sulfone were determined by means of high-pressure liquid chromatography (HPLC). Plasma samples were prepared for HPLC using disposable cartridges to perform solid-phase extraction. Each cartridge was conditioned by washing with 3 ml of methanol followed by 2 ml of water and 2 ml of 0.1 M potassium phosphate buffer (pH 6.0). To 1.1 ml of plasma, a volume of 1.1 ml of potassium phosphate buffer was added. Two milliliters of this mixture were then added to the cartridge, which was successively washed with 5 ml of water and 3 ml of 10% methanol. Five milliliters of methanol was then added, and the eluate was collected and evaporated under a stream of air at 50 C. The pellet was dissolved in 100 µL of the eluent, and 50 µL was injected into the HPLC system. Plasma standards of fenbendazole, oxfendazole, and fenbendazole sulfone were prepared from stock solutions in dimethyl sulfoxide and prepared in the same way.

The HPLC system was equipped with an autosampler, 2 HPLC pumps, and a UV detector set at 294 nm.

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Chromatography was performed, using a guard column with 40-µm particles and a reverse-phase column maintained at 40 °C. The mobile phase was a mixture of acetonitrile and 0.025 M ammonium acetate adjusted to pH 7.2 and with 345 µl of additional dibutylamine per liter. The flow rate was 1 ml/min. The proportion of acetonitrile was 30% for the first 3 minutes, progressing linearly to 40% at 3.5 minutes. This was maintained until 11 minutes, at which time the proportion was changed linearly to 30% at 11.5 minutes. This proportion of acetonitrile remained constant for the remainder of the run time (17 minutes). Under these conditions, retention times of fenbendazole, oxfendazole, and fenbendazole sulfone were 12.2, 2.7, and 4.5 minutes, respectively. The limit of quantification for fenbendazole, oxfendazole, and fenbendazole sulfone in plasma was 0.01 µg/ml. Mean ± SD recoveries of fenbendazole, oxfendazole, and fenbendazole sulfone at concentrations of 0.1 and 1.0 µg/ml were 93.1 ± 4.2% and 93.1 ± 1.9% (fenbendazole), 88.1 ± 3.3% and 87.1 ± 7.9% (oxfendazole), and 90.9 ± 2.6% and 93.6 ± 3.6% (fenbendazole sulfone). Coefficients of variation are not available.

Data analyses—Plasma concentrations of fenbendazole, oxfendazole, and fenbendazole sulfone for each pig were analyzed by use of noncompartmental procedures. The area under the plasma concentration versus time curve (AUC) and the area under the curve of the product of time and plasma concentration versus time (ie, area under the first moment, AUMC) were calculated according to the trapezoidal rule. For fenbendazole, the area under the concentration versus time curve from the time that fenbendazole was last detected in plasma samples (C last) to infinity was estimated as C last/λ, with λ defined as the slope of the terminal phase of the curve and calculated on the basis of at least 4 data points. For oxfendazole and fenbendazole sulfone, AUC was calculated only from time zero to the last detectable concentration in plasma. Mean residence time (MRT) was calculated according to the equation MRT = AUMC/AUC. The volume of distribution at steady state (V ss) was calculated from the equation V ss = D IV/Cl B, where D IV is the dose of fenbendazole administered IV. Body clearance (Cl B) was calculated from the equation Cl B = D IV/AUC. Mean absorption time after oral administration (MAT) was calculated from the equation MAT = MRT PO − MRT IV. Bioavailability (F) of fenbendazole after oral administration was estimated by the method of corresponding areas with correction for dose: using the equation F = AUC PO/AUC IV × D PO/D IV. Peak plasma concentrations (C max) and times to reach C max (T max) for fenbendazole and its metabolites were determined by visual inspection of the individual plasma concentration versus time curves.

Results—Pigs did not tolerate injection of large volumes of the mixture of dimethyl sulfoxide and propylene glycol; therefore, the dose administered IV was reduced to a fifth of the recommended dose for oral administration. The concentration of fenbendazole in plasma decreased rapidly after IV administration, and the drug was detectable only up to 6 hours after administration (Fig 1). For fenbendazole, mean AUC was 0.75 µg•h/ml, Cl B was 1.36 L/h/kg, V ss was 3.35 L/kg, and MRT was 2.63 hours (Table 1). Following oral administration, fenbendazole was detected in plasma for up to 24 hours (Fig 2), and C max and T max were 0.07 µg/ml and 3.75 hours, respectively (Table 2). The AUC for fenbendazole after oral administration was 1.60 µg•h/ml, and MRT was 15.15 hours. Bioavailability following oral administration was 27.1%.

Figure 1—Plasma concentrations of fenbendazole (FBZ), oxfendazole (OFZ), and fenbendazole sulfone (FBZ-SO2) after IV administration of fenbendazole (1 mg/kg) to 4 pigs. Values represent mean ± SD.

Table 1—Pharmacokinetic variables for fenbendazole and its metabolites oxfendazole and fenbendazole sulfone after intravenous administration of fenbendazole at a dose of 1 mg/kg to 4 pigs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fenbendazole</th>
<th>Oxfendazole</th>
<th>Fenbendazole sulfone</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg•h/ml)</td>
<td>0.75 ± 0.15</td>
<td>6.15 ± 1.60</td>
<td>2.28 ± 0.31</td>
</tr>
<tr>
<td>% of Total AUC</td>
<td>84.2 ± 2.3</td>
<td>66.5 ± 3.6</td>
<td>25.1 ± 1.6</td>
</tr>
<tr>
<td>Cl B (L/h/kg)</td>
<td>2.69 ± 1.65</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>2.63 ± 1.56</td>
<td>9.43 ± 1.13</td>
<td>17.41 ± 1.61</td>
</tr>
<tr>
<td>C max (µg/ml)</td>
<td>1.36 ± 0.26</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vss (L/kg)</td>
<td>3.35 ± 1.30</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cl B, mean</td>
<td>0.72 ± 0.04</td>
<td>0.42 ± 0.10</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>NA</td>
<td>3.25 ± 0.49</td>
<td>22.50 ± 7.54</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD. AUC = area under plasma concentration versus time curve for fenbendazole; AUC PO was extrapolated from time zero to infinity; for oxfendazole and fenbendazole sulfone, AUC were calculated from time zero to the last detectable concentration of the compound in plasma. Total AUC = sum of AUC for the 3 compounds. T EL = Terminal elimination half-life. NA = Not applicable. MRT = Mean residence time. Cl B = Body clearance. Vss = Steady state volume of distribution. C max = Maximum plasma concentration. T max = Time to achieve maximum plasma concentration.

Figure 2—Plasma concentrations of FBZ, OFZ, and FBZ-SO2 after oral administration of fenbendazole (5 mg/kg) to 4 pigs. Values represent mean ± SD.
fenbendazole, and Tmax was 22.5 hours. Forty-eight detected in plasma 2 hours after IV administration of respectively (Table 1). Fenbendazole sulfone was fenbendazole (Fig 2); Cmax and T max of oxfendazole of oxfendazole always exceeded the concentration of fone in plasma were below the limit of quantification.

concentrations of oxfendazole and fenbendazole sul-

fonic acid concentrations of fenbendazole and oxfendazole after oral administration of fenbendazole were 0.66 µg/ml and 12.5 hours, respectively (Table 2). The concentration of fenbendazole sulfone in plasma increased more slowly after oral administration of fenbendazole and peaked at 28.5 hours. The concentrations of oxfendazole and fenbendazole sulfone were below the limit of quantification in plasma samples obtained 72 hours after administration of fenbendazole. Regardless of whether fenbendazole was administered IV or PO, oxfendazole was the main component detected in plasma, accounting for two-thirds of the total AUC (ie, the sum of the AUC for fenbendazole, oxfendazole, and fenbendazole sulfone). Fenbendazole accounted for 8.4% of the total AUC after IV administration and 4.9% after oral administration.

Discussion

Results of the present study indicate that fenben-
dazole was rapidly eliminated from plasma following IV administration to pigs, with Cl of 1.36 L/h/kg. This elimination rate is more rapid than rates reported for cattle (0.17 L/h/kg), goats (0.26 L/h/kg), rabbits (0.60 L/h/kg), turkeys (0.68 L/h/kg), and chickens (1.11 L/h/kg), possibly, at least in part, because of the lower dose of fenbendazole used in the present study (1 mg/kg), compared with the previous study (5 mg/kg). The V∞ of fenbendazole in pigs in the present study (3.35 L/kg) corresponded with volumes reported for other species (2.14 to 4.62 L/kg). In cattle, V∞ of another thiosubstituted benzimidazole, albendazole, was 3.39 L/kg. Bioavailability of fenbendazole after oral administration to pigs in the present study was 27.1%. For comparison, values reported for cattle, goats, rabbits, chickens, and turkeys are 20.8, 23.5, 18.0, 16.0, and 10.0%, respectively. Most studies of the pharmacokinetic behavior of fenbendazole have been performed in sheep and cattle. The special digestive physiology of the ruminant gastrointestinal tract makes it difficult to compare certain pharmacoki-
netic variables for ruminants with variables for non-
ruminants such as pigs. The rumen acts as a reservoir for orally administered benzimidazoles, from which the drug is slowly released, resulting in prolonged plasma concentrations of the parent drug and metabolites. Accordingly, Tmax for fenbendazole and its metabolites in ruminants are generally greater than the values found for pigs in the present study.

Pharmacokinetics of fenbendazole following oral administration in pigs have been studied previously. Values for Cmax, Tmax, and AUC of fenbendazole reported in that study (0.45 µg/ml, 10 hours, and 14 µg•h/ml, respectively) were greater than those found in the present study. This may possibly be explained by differences between analytical methods used in the 2 studies. The assay used by Düwel et al may not have differentiated fenbendazole from its metabolites, and values reported may represent values for fenbendazole, oxfendazole, and fenbendazole sulfone combined. Pharmacokinetics of fenbendazole following oral administration to dogs have been reported. After administration of fenbendazole at a dose of 5 mg/kg, Cmax and Tmax were 0.16 µg/ml and 5.6 hours, which were comparable to values obtained for pigs in the present study.

The rapid appearance of oxfendazole followed by fenbendazole sulfone in the plasma of pigs after IV administration of fenbendazole reflects the sequential metabolic pathway of fenbendazole. The pattern of metabolism of fenbendazole is reflected in the percent-
ages of total AUC accounted for by each compound. After oral administration, fenbendazole accounted for 4.5% of the total AUC in these pig. In sheep, fenbendazole accounted for 8 and 33% of total AUC. In cattle, the corresponding value was 27 to 33% and in dog, fenbendazole accounted for approximately 50% of the total AUC, but AUC for only fenbendazole and oxfendazole were reported. The low value found in the present study is consistent with the rapid clear-
face of fenbendazole in pigs. The nonrandomized order of drug administration used in the present study (all pigs had fenbendazole administered by IV route first) possibly contributed to these large species differences owing to effects on drug metabolizing enzymes. Still, when incubated with febantel or fenbendazole, hepatic microsomes from pigs produced greater amounts of oxfendazole than did hepatic microsomes from cattle. After oral administration of albendazole to pigs, Alvarez et al reported a ratio of plasma AUC for albendazole sulfoxide:albendazole sulfone of 1.9. In the present study, the ratio of plasma AUC for oxfendazole:fenbendazole sulfone was 2.2, indicating similar metabolic patterns for albendazole and fenbendazole in pigs.

Table 2—Pharmacokinetic variables for fenbendazole and its metabolites oxfendazole and fenbendazole sulfone after oral administration of fenbendazole at a dose of 5 mg/kg to 4 pigs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fenbendazole</th>
<th>Oxfendazole sulfone</th>
<th>Fenbendazole sulfone</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg•h/ml)</td>
<td>1.00 ± 0.24</td>
<td>15.61 ± 5.24</td>
<td>7.04 ± 3.08</td>
</tr>
<tr>
<td>% of Total AUC</td>
<td>45.1 ± 16.5</td>
<td>65.9 ± 10.0</td>
<td>29.7 ± 10.6</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>8.38 ± 4.28</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>15.15 ± 6.76</td>
<td>17.05 ± 3.79</td>
<td>27.23 ± 2.81</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>12.52 ± 5.93</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>0.07 ± 0.04</td>
<td>0.66 ± 0.22</td>
<td>0.24 ± 0.09</td>
</tr>
<tr>
<td>F (%)</td>
<td>2.71 ± 10.8</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

MAT = Mean absorption time. F = Bioavailability. See Table 1 for remainder of key.
References