Pharmacokinetics and Bioavailability of the Anti-Human Immunodeficiency Virus Nucleotide Analog 9-[(R)-2-(Phosphonomethoxy)Propyl]Adenine (PMPA) in Dogs

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The pharmacokinetics, bioavailability, and metabolism of the anti-human immunodeficiency virus nucleotide analog 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) were determined in beagle dogs following intravenous, intraperitoneal, and oral administration. Fasted male beagle dogs (n = 5) were pretreated with pentagastrin and received PMPA (10 mg/kg of body weight) by the intravenous and oral routes with a washout period of 1 week between doses. A further group of male dogs received PMPA as a single dose via the intravenous (1 mg/kg; n = 5) and the intraperitoneal (10 mg/kg; n = 3) routes, with 1-week washout period between doses. The concentrations of PMPA in plasma and urine were determined over 48 h post dosing by fluorescence derivatization and high-performance liquid chromatography (HPLC). The potential for metabolism or biliary excretion of PMPA was evaluated in a dog with a chronic indwelling bile cannula. Urine, feces, and bile were collected at intervals over 48 h following the intravenous administration of [14C]PMPA (10 mg/kg; 55 μCi/kg). The concentrations of PMPA in plasma after intravenous injection were best described by an open two-compartment model with a terminal half-life of approximately 10 h. PMPA was excreted unchanged in urine (70%); recovery in feces (0.42%) or bile (0.26%) was negligible. The plasma clearance of PMPA (0.28 ± 0.05 liter/h/kg) was substantially greater than the glomerular filtration rate in this species, suggesting active tubular secretion of PMPA. No metabolites of [14C]PMPA were observed in urine, feces, or bile on the basis of HPLC with radioactive flow detection. The remainder of the dose was probably excreted unchanged in urine beyond 48 h post dosing. The mean ± standard deviation observed bioavailabilities of PMPA following oral and intraperitoneal administration at 10 mg/kg were 17.1% ± 1.88% and 73.5% ± 10.5%, respectively.

MATERIALS AND METHODS

Materials. PMPA monohydrate and adefovir were obtained from Gilead Sciences, Inc. (Foster City, Calif.). [8-14C]PMPA (lot 117-303-026; specific activity, 26 μCi/mmol) was obtained as a solution in ethanol-water (70:30) from Moravek (Brea, Calif.). There were no detectable impurities in the radioactive material on the basis of high-performance liquid chromatography (HPLC) with radioactive flow detection. Pentagastrin (Peptavlon; 0.25 mg/ml) was obtained from Ayerst Laboratories, Inc. (Philadelphia, Pa.). Tetrabutylammonium dihydrogen phosphate (TBAHP) was obtained from Fluka (Ronkonkoma, N.Y.). Acetonitrile was from Burdick and Jackson (Muskegon, Mich.). Chloroacetaldehyde and trifluoroacetic acid were from Aldrich (Milwaukee, Wis.). All other chemicals were from Mallinckrodt (Phillipsburg, N.J.).

Formulations. Unlabelled PMPA monohydrate was formulated for intravenous or intraperitoneal administration as a sterile aqueous solution in water for injections, and the solution was adjusted to pH 7.4 with 1 N sodium hydroxide. Solutions containing 5 and 50 mg of PMPA/ml were prepared and were sterilized by filtration with a 0.2-μm-pore-size Acrodisc 13 filter (Gelman Sciences, Ann Arbor, Mich.). The dose for both solutions was 0.2 ml/kg (equivalent to 1.0 or 10 mg of PMPA/kg). An oral formulation of PMPA containing 10 mg of PMPA/ml in 0.9% sodium chloride was prepared. The dose was 1 ml/kg (equivalent to 10 mg of PMPA/kg). Radiolabelled PMPA was formulated for intravenous administration as a sterile solution in water for injections containing 50 mg of PMPA/ml (277 μCi of [14C]PMPA/ml). The pH of the solution was adjusted to 7.5 with 1 N sodium hydroxide, and the solution was sterilized by filtration through a 0.2-μm-pore-size filter. The dose volume was 0.2 ml/kg (equivalent to 10 mg of PMPA/kg; 55 μCi/kg).

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9-[(R)-2-(Phosphonomethoxy)propyl]adenine (PMPA) (Fig. 1) is an analog of dAMP with potent activity against retrovirus replication (1). PMPA has been proven to be effective in preventing the establishment of simian immunodeficiency virus (SIV) infection in rhesus macaques, even when the drug was given up to 24 h after intravenous inoculation with the virus (17). The monkeys, which were treated postinfection with subcutaneous PMPA at a dose of 30 mg/kg of body weight for 28 days, showed no signs of infection after 1 year of intensive follow-up (including PCR of proviral DNA and biopsy of inguinal lymph nodes). In the same study, zidovudine failed to protect the animals from SIV infection. Intravenous PMPA has also been proven to be effective in preventing vertical (male-to-female) transmission of the virus (10). Unlike nucleoside analogs such as zidovudine, PMPA possesses a metabolically stable phosphonoether moiety that does not require phosphorylation by viral kinases to be activated. The drug is phosphorylated by cellular enzymes to form the active metabolite, PMPA diphosphate (9).

PMPA has been proven to be stable to enzymatic degradation in vitro in animal and human tissues (15). Following intravenous administration of 10 mg of [14C]PMPA per kg to rats, more than 92% of the dose was recovered unchanged in urine and 4.5% was recovered unchanged in feces 7 days post dosing. The fecal recovery was significantly higher when the dose was increased to 50 mg/kg (6). The purpose of the present study was to examine the pharmacokinetics and metabolism of PMPA in dogs to support further clinical development. In addition, the oral bioavailability of the drug was examined to determine the value of an alternative route of administration in future clinical studies. The data for PMPA obtained following oral administration were also compared to those obtained following intraperitoneal administration.
Study design. (i) Animals. The in-life phase of this study was conducted in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals (8a) and was approved by the Institutional Animal Care and Use Committee. Two groups of five adult male beagle dogs were used for the pharmacokinetic study. The mean body weight at the time of administration of the first intravenous dose was 9.1 ± 0.3 kg (range, 8.7 to 9.5 kg). The animals were conscious throughout the entire study and were acclimated to the blood collection procedure. The dogs were housed in stainless-steel metabolism cages during all urine collection periods and were fasted 12 to 18 h prior to dosing and until 6 h postdosing. In order to simulate the pH of the human intestinal tract, the dogs were pretreated with a single intramuscular injection of pentagastrin at a dose of 6 μg/kg, 20 min prior to PMPA dosing. Water was provided ad libitum.

(ii) Drug administration. Five male beagle dogs (group 1) received a single intravenous dose of PMPA (10 mg/kg) by a cephalic vein. Following a 1-week washout period, the same dogs received a single oral dose of PMPA (10 mg/kg) by gavage, followed by two 10-ml water washes. A second group of five male beagle dogs (group 2) received a single intravenous dose of PMPA (1 mg/kg) via a cephalic vein. Following a 1-week washout period, three of these dogs received a single intraperitoneal injection of PMPA (10 mg/kg).

(iii) Sample collection. Blood samples (4.0 ml) were collected from each animal by direct jugular access and placed into heparinized tubes. The samples were collected at 0 (predose), 5, 15, 30, and 45 min and 1, 2, 4, 6, 8, 12, and 24 h postdosing. The animals remained conscious throughout the sample collection period. The blood was chilled and was immediately processed by centrifugation at 2,000 × g for 10 min to obtain the plasma. The plasma samples were frozen and were maintained at −20°C until they were analyzed. Urine samples were collected over intervals of 0 to 24 and 24 to 48 h. Aliquots of urine samples were mixed on the basis of the total volume collected. The combined samples were then analyzed to determine the total amount of PMPA recovered from urine during the first 48 h postdosing.

(iv) Determination of PMPA in plasma and urine. The concentrations of PMPA in plasma and urine samples were determined by derivatization and HPLC analysis with fluorescence detection. Adefovir was used as the internal standard for both analyses. PMPA and adefovir each react with chloroacetaldehyde to yield highly fluorescent 6-ethenoadenine derivatives (8). Plasma (200 μl) and internal standard (20 μl of 10 μg of adefovir/ml, providing a final adefovir concentration of 1 μg/ml) were mixed with 400 μl of acetonitrile containing 0.1% trifluoroacetic acid to precipitate protein. The samples were then evaporated to dryness under reduced pressure at room temperature in a SpeedVac (Savant Instruments, Farmingdale, N.Y.). Urine samples (20 μl) and internal standard (30 μl of 10 μg of adefovir/ml, providing a final adefovir concentration of 1.5 μg/ml) were used directly for derivatization without drying. Dried plasma samples or urine samples were reconstituted in 200 μl of derivatization cocktail (0.34% chloroacetaldehyde in 100 mM sodium acetate [pH 4.5]), vortexed, and centrifuged at 15,000 × g in an Eppendorf Centrifuge 5402 for 10 min. The supernatant was transferred to a clean screw-cap tube and incubated at 95°C for 40 min. Derivatized samples were quenched on ice and evaporated to dryness under reduced pressure at room temperature in a SpeedVac (Savant Instruments, Farmingdale, N.Y.). The filtrate was analyzed directly by HPLC. The HPLC system comprised a model P4000 solvent delivery system with a model AS3000 autoinjector and a model UV/1000 UV detector (Thermo Separations, San Jose, Calif.). A Zorbax RX C-18 reverse-phase column (150 by 4.6 mm; MAC-MOD, Chadds Ford, Pa.) equipped with a Brownlee RP-18 Newguard guard column (7 μm; 15 by 3.2 mm; Alltech, Deerfield, Ill.) was used. The following mobile phases were used: mobile phase A, 6% acetonitrile in 20 mM potassium phosphate buffer with 5 mM TBAHP (pH 6.0), and mobile phase B, 65% acetonitrile in 20 mM potassium phosphate buffer with 5 mM TBAHP (pH 6.0). The flow rate was 1.5 ml/min, and the column temperature was maintained at 35°C with a column oven. The gradient profile was 100% mobile phase A until 8.0 min and then a linear gradient to 100% mobile phase B for 20 min, at which time there was an immediate return to 100% mobile phase A. Detection was by fluorescence with excitation at 236 nm and emission at 420 nm, and the injection volume was 50 μl. The total cycle time between injections was 25 min. Data were acquired and stored with a Peak Pro data acquisition system (Beckman, Palo Alto, Calif.). The analytical method for PMPA in plasma was linear over the range of 25 to 1,000 ng/ml, and the lower limit of quantitation was 25 ng/ml. The within-day precision and accuracy (deviation from nominal) were <10% and <12%, respectively.

(v) Pharmacokinetic calculations. Data for intravenous PMPA were analyzed by application of a two-compartment model with the nonlinear curve-fitting software, PCNONLIN (16) (weighted by using 1/y). The corresponding pharmacokinetic parameters were calculated for the biexponential equation (CP(D) = A · e−μt + B · e−βt), where CP(D) is the concentration of drug in plasma at time t; A and B are the intercepts and exponents, respectively, of the two exponential phases.

(vi) Pharmacokinetic calculations. Data for the oral and intraperitoneal routes were analyzed initially by noncompartmental methods. A minimum of three datum points were used to determine the half-life of the terminal phase. Additional parameters were calculated manually. For the intraperitoneal (i.p.) route, the bioavailability was calculated as 100 · [AUC(i.p.)/AUC(i.v.)] · (AUC(i.v.)/AUC(i.p.)) (where i.v. is the area under the concentration-time curve [AUC] from time zero to infinity) by using data obtained with the same animals after the administration of 1 mg/kg by the intravenous (i.v.) route. Oral bioavailability was calculated in an analogous manner using data obtained with the same animals after the administration of 10 mg/kg by the intravenous route. Pharmacokinetic parameters for PMPA administered orally and intraperitoneally were also confirmed by application of a two-compartment model with a first-order absorption phase.

(vii) Metabolism and excretion of PMPA. A pilot study was conducted to assess the possibility of biliary excretion of PMPA. A single dog with an indwelling chronic Bile Access System (Access Technologies, Skokie, Ill.) was given an intravenous dose of [14C]PMPA at 10 mg/kg (55 μCi/kg). The bile access system consisted of a modified t-tube device designed to allow access to bile without permanent interruption of normal bile flow. The device was connected to two subcutaneous access ports: one for a balloon catheter within the t-tube assembly and one for the bile sampling tube itself. When saline was introduced to inflate the balloon catheter, the normal bile flow was blocked and was diverted into the sampling tube. PMPA was administered by intravenous injection into a peripheral vein. Bile, urine, and feces were collected continuously at intervals over a 48-h period. The total radioactivity in these tissues was determined by sample oxidation and liquid scintillation. Duplicate aliquots (∼200 μl) of plasma, urine, or bile were pipetted onto Combustone combi inserts and were oxidized with a model 307 sample oxidizer (Packard, Meriden, Conn.). Fecal samples were homogenized in water (20% [wt/vol]) prior to combustion. The resulting samples were counted on a TriCarb model 2500 liquid scintillation counter (Packard). The combined recovery from the oxidation and liquid scintillation steps was 94% with commercial 14C-labelled standards.

(viii) Radiochromatography of urine and bile samples. The presence of intact [14C]PMPA and potential metabolites in urine or bile samples was determined by ion-exchange HPLC with radioactive flow detection. Samples of urine or bile (0.5 ml) were transferred to 0.2-μm Z-spin Plus filter units (Alltech) and centrifuged at 16,000 × g for 20 min at 4°C. The filtrate was analyzed directly by HPLC. The HPLC system comprised a model P4000 solvent delivery system with a model AS3000 autoinjector and a model UV/1000 UV detector (Thermo Separations). A Zorbax RX C-18 reverse-phase column (150 by 4.6 mm; MAC-MOD) was equipped with a Brownlee RP-18 Newguard guard column (7 μm; 15 by 3.2 mm; Alltech) was used. The following mobile phases were used: mobile phase A, 5% acetonitrile and 20 mM potassium phosphate (pH 5.5) containing 5 mM TBAHP, and mobile phase B, 65% acetonitrile and 20 mM potassium phosphate (pH 5.5) containing 5 mM TBAHP. The gradient profile was 100% mobile phase A to 100% mobile phase B over 15 min, at which time there was a return to mobile phase A for 10 min. The cycle time was 25 min. The flow rate was 1.5 ml/min and the column temperature was maintained at 40°C with a column oven (Shimadzu, Columbia, Md.). The injection volume was 25 μl. Detection was with a Radiomatic FLO-ONE/Beta radioactive flow detector (Packard Series A-500), with FLO-SCINT A (Packard) used as the scintillation fluid. UV detection with absorption at 262 nm was also used. The data were acquired and stored with a FLO-ONE data acquisition system (Packard). The efficiency of the radioactivity detection system was >90% for carbon-14.

RESULTS AND DISCUSSION

Figure 2 presents the time course of PMPA concentrations in plasma following the intravenous administration of PMPA to beagle dogs at 1.0 and 10 mg/kg. The data for the 10-mg/kg dose were well described by a two-compartment open model with a weighting factor of 1. The model was selected on the basis of the Akaiki information criterion and examination of scatter plots of the residual error. Table 1 summarizes the values of the pharmacokinetic parameters for intravenous PMPA obtained with this model. The apparent half-life after administration of the 1-mg/kg dose appeared to be shorter.

FIG. 1. Chemical structure of PMPA.
Data obtained after administration of the 10-mg/kg dose. The lines are the simulated data obtained by using the parameters derived from compartmental analysis of the data obtained after administration of the 10-mg/kg dose.

than that after administration of the 10-mg/kg dose (P = 0.001; unpaired t test), suggesting possible saturation of renal clearance. However, the difference in half-lives between the 1- and 10-mg/kg doses was probably an artifact of the constraints of the analytical method (PMPA was not detectable beyond 12 h postdosing for the 1-mg/kg dose, whereas the drug was detectable at 24 h postdosing for the 10-mg/kg dose). The parameters of the two-compartment model derived for the 10-mg/kg dose were therefore used to simulate the pharmacokinetics of intravenous PMPA at 1 mg/kg (Fig. 2). On the basis of that simulation, the calculated data for the 1-mg/kg dose were consistent with the detectable datum points. In addition, the dose-normalized values of either AUC or the maximum concentration of drug in serum (C_max) for the 1- and 10-mg/kg doses were not significantly different (P > 0.08). These observations suggest that the pharmacokinetics of PMPA were independent of dose over the dose range of 1 to 10 mg/kg. The clearance of PMPA (281 ± 51.3 ml/h/kg) exceeded the glomerular filtration rate in this species (160 ml/h/kg) (11), indicating the possibility of active tubular secretion. This property appears to be characteristic of all other nucleotide analogs examined to date. Urinary recovery in 48 h for the 10-mg/kg dose (70.0%, on the basis of measurement of radioactivity) was significantly lower than that for the 1-mg/kg dose (84.3%). However, this was possibly the result of incomplete urine collection. All radioactivity present in urine and bile was attributed to PMPA; no metabolites of PMPA were detected on the basis of radiochromatography.

The values of the noncompartmental pharmacokinetic parameters for PMPA administered orally and intraperitoneally are summarized in Table 2. Table 2 also presents the corresponding pharmacokinetic parameters derived from a two-compartment model with a first-order absorption phase. The data obtained by the two methods were similar. The mean ± standard deviation (SD) absolute oral bioavailability of PMPA in dogs was 17.1% ± 1.88% on the basis of a comparison with the data obtained after intravenous administration of 10 mg/kg to the same animals. The urinary recovery of the administered dose at 48 h postdosing was 20.5% following oral administration. These data suggest that all of the absorbed PMPA dose is ultimately excreted in the urine. The mean C_max following oral administration of PMPA was >30-fold lower than that following intravenous administration of the same dose (Fig. 3). The mean ± SD observed bioavailability of PMPA following the intraperitoneal administration of 10 mg/kg was 73.5% ± 10.5% (on the basis of a comparison with the data obtained after the intravenous administration of PMPA at 1 mg/kg to the same dogs). The urinary recovery of PMPA following intraperitoneal administration was 62.5% ± 14.5% of the dose. A drug administered by intraperitoneal injection is primarily taken up by blood vessels that drain into the hepatic portal vein. Therefore, intraperitoneal delivery of PMPA is subject to the same potential hepatic first-pass losses as oral administration. The intraperitoneal bioavailability of PMPA greatly exceeded that of orally administered drug, indicating that the oral bioavailability of PMPA is primarily limited by its low level of intestinal permeation. However, the less than complete bioavailability of intraperitoneal PMPA may be the result of some contribution of hepatic clearance, a delayed efflux of a portion of the administered PMPA from the peritoneal cavity, or inadvertent injection of a portion of the administered drug directly into the intestinal lumen. The bioavailability of oral PMPA in dogs (17.1%) was higher than expected on the basis of data obtained from studies with rats or monkeys. The oral bioavailabilities of other nucleotide analogs (e.g., cidofovir and adefovir) have also been unexpectedly high in dogs (12, 15), suggesting that an active transport system for this class of compounds may exist in the intestine of the dog. However, the dog has been used successfully to identify oral prodrugs of nucleotide analogs (12, 14) that have similar bioavailabilities in humans.

Following the intravenous administration of [14C]PMPA, the recovery of the radioactive dose in bile was negligible (<0.3% at 48 h). The fecal recovery of radioactivity was also low (0.42% at 48 h). The urinary recovery of PMPA in this experiment was 51.9% at 24 h and 70.0% at 48 h. These results suggest that the remainder of the PMPA dose was probably excreted in the urine beyond 48 h.

The pharmacokinetics of adefovir (9-[(R)-(1-phosphono- methoxy)ethyl]adenine), a structural analog of PMPA lacking a methyl side chain, have been examined in animals (4, 9, 13) and humans (5). Adefovir is cleared by a combination of glomerular filtration and tubular secretion. The terminal half-life for intravenous PMPA in dogs was 9.54 ± 1.21 h, which is somewhat longer than that observed previously for intravenous adefovir for dogs given the same dose (6.6 ± 0.4 h) (15).

![FIG. 2. Time course of PMPA concentrations in dog plasma following intravenous administration (○, 1 mg/kg; ●, 10 mg/kg). The data depicted here are for five individual animals receiving each dose. The lines are the simulated data obtained by using the parameters derived from compartmental analysis of the data obtained after administration of the 10-mg/kg dose.](http://aac.asm.org/)

<table>
<thead>
<tr>
<th>PMPA dose (mg/kg)</th>
<th>AUC_0-∞ (µg · h/ml)</th>
<th>C_max (µg/ml)</th>
<th>MRT (h)</th>
<th>CL (ml/h/kg)</th>
<th>VSS (ml/kg)</th>
<th>Terminal t_1/2 (h)</th>
<th>% Dose recovered in urine at 48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>2.87 (0.40)</td>
<td>3.27 (0.27)</td>
<td>2.62 (0.94)</td>
<td>353 (47.2)</td>
<td>899 (238)</td>
<td>4.51 (1.94)</td>
<td>84.3 (4.53)</td>
</tr>
<tr>
<td>10.0</td>
<td>36.7 (7.94)</td>
<td>33.1 (6.39)</td>
<td>6.21 (0.75)</td>
<td>281 (51.3)</td>
<td>1,740 (329)</td>
<td>9.54 (1.21)</td>
<td>50.6 (12.5)</td>
</tr>
</tbody>
</table>

* Values are means (SDs) for five animals. Abbreviations: C_max, concentration extrapolated to zero time; MRT, mean residence time; CL, clearance; VSS, volume of distribution at steady state; t_1/2, half-life.
Reanalysis of the data for adefovir by the same two-compartment model applied to PMPA gave a terminal half-life for adefovir of 7.28 ± 1.18 h. This value is significantly less than that for PMPA (P = 0.017; unpaired t test). However, the total clearance of PMPA from the plasma of dogs (0.281 ± 0.051 liter/h/kg) was not significantly different from that observed for intravenous adefovir at the same dose (0.347 ± 0.067 liter/h/kg) (P = 0.119). These data suggest that the extent of tubular secretion of PMPA is similar to that observed for adefovir.

In summary, the pharmacokinetics of intravenous PMPA in beagle dogs were independent of dose over the dose range of 1 to 10 mg/kg. PMPA was excreted unchanged in urine by a combination of filtration and tubular secretion, and recovery in bile or feces was negligible. The relatively long half-life of intravenous PMPA appears to be consistent with once-daily dosing. The oral bioavailability of PMPA was limited by the low level of permeation of the drug. Despite this, oral absorption of PMPA in the dog was greater than expected, possibly as a result of an active transport system in the dog intestine. Other members of the phosphonate nucleotide analog class have been shown to have lower bioavailabilities in humans than in dogs, and low bioavailability is anticipated for PMPA in humans (2). These observations have led to the design of a novel bioavailable prodrug of PMPA that can be administered as a solid oral dosage form, compatible with current clinical therapy of human immunodeficiency virus infection (3).

FIG. 3. Time course of PMPA concentrations in dog plasma following intravenous (n = 5), oral (n = 5), or intraperitoneal (n = 3) administration of 10 mg/kg (○, intravenous; □, intraperitoneal; ■, oral). Data are means ± SDs.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Analysis method</th>
<th>$C_{max}$ (µg/ml)</th>
<th>$T_{max}$ (h)</th>
<th>AUC (µg · h/ml)</th>
<th>Terminal $t_{1/2}$ (h)</th>
<th>Bioavailability (%)</th>
<th>% Dose recovered in urine at 48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (n = 5)</td>
<td>NC</td>
<td>1.29 (0.54)</td>
<td>1.00 (0.00)</td>
<td>6.38 (2.08)</td>
<td>7.31 (3.04)</td>
<td>17.1 (1.88)</td>
<td>20.5 (5.13)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1.09 (0.43)</td>
<td>1.06 (0.15)</td>
<td>6.78 (2.49)</td>
<td>9.49 (3.56)</td>
<td>18.5 (6.79)</td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal (n = 3)</td>
<td>NC</td>
<td>9.69 (2.11)</td>
<td>0.42 (0.14)</td>
<td>19.3 (5.38)</td>
<td>7.23 (1.35)</td>
<td>73.5 (10.5)</td>
<td>62.5 (14.5)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>9.71 (2.43)</td>
<td>0.38 (0.21)</td>
<td>17.7 (4.74)</td>
<td>4.97 (3.56)</td>
<td>67.4 (15.4)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2. Pharmacokinetic parameters for oral and intraperitoneal PMPA at 10 mg/kg in male beagle dogs

* Values are means (SDs). Bioavailability was calculated by using data obtained after the intravenous administration of PMPA to the same animals. Abbreviations: NC, noncompartmental analysis; C, two-compartment model; $T_{max}$, time to $C_{max}$; $t_{1/2}$, half-life.

REFERENCES