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THE PHARMACOKINETICS OF ORALLY ADMINISTERED IVERMECTIN IN AFRICAN ELEPHANTS (*LOXODONTA AFRICANA*): IMPLICATIONS FOR PARASITE ELIMINATION

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Abstract: *Loxodonta africana* are susceptible to a wide variety of parasites that are often treated with the broad spectrum antiparasitic ivermectin (IVM) based on empirical knowledge. The objectives of this study were to 1) measure plasma IVM levels following administration of 0.1 mg/kg IVM p.o., 2) compare plasma IVM levels following administration with regular versus restricted feed rations, 3) measure IVM excretion in feces, and 4) use these findings to generate dosing recommendations for this species. Using a crossover design, six African elephants were divided into two groups. Ivermectin was administered and typical grain rations were either provided or withheld for 2 hr. Blood and fecal samples were collected for 7 days following drug administration. After a 5-wk washout period, groups were switched and the procedure repeated. Plasma and fecal IVM were analyzed using high-performance liquid chromatography. There was no statistically significant difference detected in the pharmacokinetic data between the fed and fasted groups. Peak plasma concentration, area under the curve, and half-life for plasma ranged between 5.41–8.49 ng/ml, 17.1–20.3 ng × day/ml, and 3.12–4.47 day, respectively. High IVM concentrations were detected in feces. The peak concentration values in feces were between 264–311-fold higher than those obtained in plasma. The comparatively large area under the curve and short time to maximum concentration in feces indicate elimination prior to absorption of much of the drug. Plasma IVM concentrations were low when compared to other species. Based on these findings, administration of 0.2–0.4 mg/kg p.o. should be appropriate for eliminating many types of parasites in elephants, and could minimize development of parasite resistance.

Key words: Anthelmintic, elephant, ivermectin, lice, *Loxodonta africana*, pharmacokinetic.

INTRODUCTION

There are a lack of pharmacokinetic–pharmacodynamic data available for African elephants for all drug categories, including parasiticides. Current dosaging recommendations in elephants are largely based on extrapolation from domestic species and on anecdotal reports of clinical efficacy. In general, extrapolation of drug dosages across species can be problematic because of many physiologic differences that can substantially affect drug absorption and distribution. For parasiticides, the proper dosages is crucial in order to optimize parasite control while minimizing development of drug resistance, because drug resistance may be associated with repeat dosing and underdosing.[37] The emergence of resistance to the antiparasitic drug ivermectin (IVM) has been shown among intestinal nematodes of sheep, goats, and cattle,[36] and more recently among arthropods such as mites and ticks.[10,26]

Ivermectin is an antiparasitic agent in the avermectin class, which consists of macrocyclic lactones that are naturally occurring fermentation products of *Streptomyces avermitilis*.[9] Ivermectin has a very broad spectrum of activity, including nematodes and arthropods.[33] The lipophilic nature of IVM results in typically high tissue concentration levels and biliary excretion.[9] The antiparasitic activity of the drug not only depends on the direct effect on the parasite, but also on reaching sustained concentrations at the target site.[19] Effects of IVM are largely dose dependent, and the target site concentration can be substantially affected by factors including species treated, dosage, formulation, and route of administration.[8,19,24] Plasma concentration of IVM is a good predictor of clinical efficacy.[23]

African elephants (*Loxodonta africana*) are susceptible to a wide variety of parasites.[35] These infections are often treated empirically with IVM, because it is effective against many external and internal parasite infections and has a large margin of safety.[33] Ivermectin is safe at up to nine times the recommended dose in horses and 29 times the recommended dose in cattle.[33] Above these levels, symptoms may include depression, ataxia, visual

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impairment, and occasional death.[33] Despite relatively common usage, there are few reports of IVM administration to elephants in the literature. One case report refers to treatment for infestation of the elephant louse (*Haematomyzus elephantis*) on African and Asian elephants, using a suggested dosage of 0.06–0.09 mg/kg IVM p.o.[17] Anecdotal reports refer to treatment of nematodes with a suggested oral or subcutaneous dosage of 0.1 mg/kg (www.elephantcare.org/Drugs/ivermect.htm). These dose recommendations are low in comparison to standard dosage recommendations of 0.2 mg/kg for domestic horses and livestock derived from numerous pharmacologic studies.[7,16,18,25,29,30] However, the dose appears to be appropriate based on metabolic scaling calculations used to extrapolate a dose from horses.

The objectives of this study were to 1) describe the pharmacokinetic behavior of IVM following administration of 0.1 mg/kg IVM p.o.; 2) compare plasma IVM levels following administration with regular versus restricted feed rations, 3) measure IVM excretion in feces, and 4) use these findings to generate dosaging recommendations for this species.

MATERIALS AND METHODS

Drug administration and sample collection

Six African elephants, including one adult male, three adult females, one juvenile male, and one juvenile female ranging from 1,300–5,000 kg comprised the study group. Using a crossover design, the elephants were divided into groups A and B, each consisting of three animals. Typical grain rations were provided (2–5 kg) along with the administration of IVM (Promectin E oral solution, Phoenix Scientific, Inc, St. Joseph, Missouri 64501, USA) for group A (full-ration group); grain rations were withheld for 2 hr following drug administration for group B (restricted-ration group). Drug administration was achieved by pouring the solution over peanut butter within two pieces of bread. Four to eight sandwiches with a total of 13–50 ml IVM were fed to each elephant. Hay and water were provided ad libitum. Blood samples (6 ml) were collected into heparinized tubes from an ear vein prior to drug administration, and at 3, 6, 9, 23, and 30 hr, and 2, 3, 4, 5, 6, and 7 day post-administration. Fecal samples (approximately 50 g) were collected into plastic bags prior to drug administration and daily for 7 day post-administration. After a 5-wk washout period, groups were reversed and the procedure repeated. These procedures were approved by the Pittsburgh Zoo and PPG Aquarium Institutional Animal Care and Use Committee.

Following blood collection, samples were centrifuged and plasma was separated and stored at −70°C for 6–8 mo prior to shipping. Fecal samples were stored at −20°C, for the same time period. Samples were shipped by air to a pharmacology laboratory (Veterinary Pharmacology Laboratory, Central University, 7000 Tandil, Argentina).

Analytic procedures

Extraction of IVM from spiked and experimental plasma and fecal samples was carried out following a technique described[22] and adapted from a previously reported method.[4] Briefly, 1-ml or 1-g aliquots of plasma and feces (wet weight), respectively, were combined with 100 μl of internal standard (abamectin, 100 ng/ml), 1 ml acetonitrile, and 0.125 ml water. The mixture was vortexed (Multi Tube Vortexer, VWR Scientific Products, West Chester, Pennsylvania 19380, USA) for 20 min. After mixing, the fecal samples were sonicated for 10 min (Transsonic 570/H, Laboratory Line Instruments Inc., Melrose Park, Illinois 60164, USA) and the solvent–sample mixture (plasma or feces) was centrifuged at 358 g for 15 min. The supernatant was manually transferred into a tube and the procedure repeated for fecal samples. The pooled supernatants obtained were then placed in an Aspec XL autosampler (Gilson, Villiers Le Bell 95400, France). Following automatic sample preparation, reconstitution was performed using a derivatization method previously described.[12] The plasma and fecal IVM concentrations were determined by high-performance liquid chromatography (HPLC) using a Shimadzu 10 A HPLC system (Shimadzu Corp., Kyoto 604-8511, Japan) and a technique previously described.[22] A complete validation of the analytic procedures for extraction and quantification of IVM was performed before starting the analysis of experimental samples from the pharmacokinetic trial. In this process, IVM-spiked standards were measured in different concentrations, in three replicate determinations. Calibration curves were established using least-squares linear regression analysis and correlation coefficients (r) and coefficient of variations (CV) were obtained. The CV was calculated as the following: (SD/mean) × 100. Drug recovery was estimated by comparison of the peak area from spiked plasma and fecal standards at different concentrations, with the peak areas resulting from direct injections of standards in methanol. The precision of the extraction and chromatographic procedures was evaluated by processing four replicate aliquots of pooled plasma and fecal samples containing known amounts of IVM (2 and 50 ng/ml or ng/g) on different working days. The limits of drug

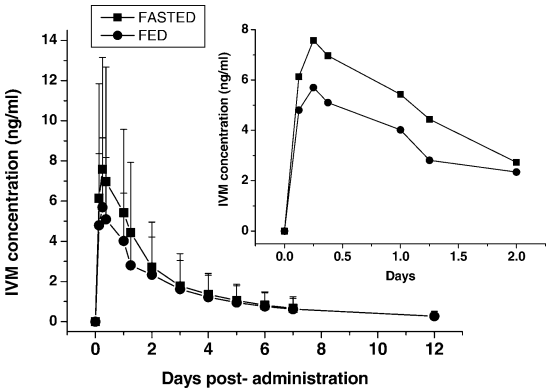

Figure 1. Mean (± SD) ivermectin plasma concentration (n = 6) obtained after its oral administration to fed and fasted African elephants (0.1 mg/kg). The insert shows the comparative plasma concentrations measured during the first 2 day after the administration of the antiparasitic compound.

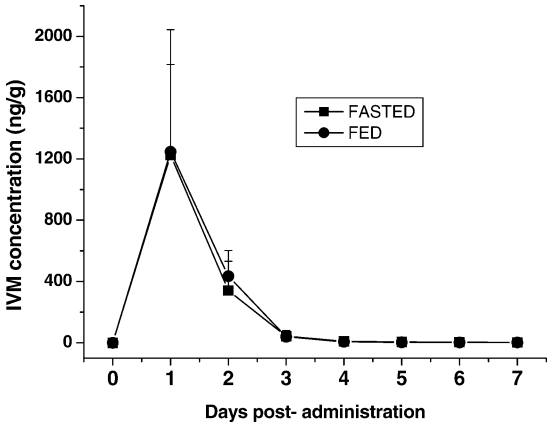

Figure 2. Mean (± SD) ivermectin fecal concentration (n = 6) obtained after its oral administration to fed and fasted African elephants (0.1 mg/kg).

detection and quantification were established. Concentration values below the quantification limit were not considered for the kinetic analysis of experimental data.

Pharmacokinetic and statistical analysis

The plasma and fecal concentrations-versus-time curves obtained after each treatment in each individual animal were fitted with the PK Solutions 2.0 (Ashland, Ohio 44805, USA) computer software. Pharmacokinetic parameters were determined using a noncompartmental model method. The peak concentration (C_{MAX}) and time to peak concentration (T_{MAX}) were read from the plotted concentration–time curve in each individual animal. The terminal (elimination) half-life ($T_{1/2}$) and absorption $T_{1/2}$ were calculated as ln 2/λz and ln 2/$k_{ab,}$ respectively, where λz is the elimination rate constant and k_{ab} represents the first-order absorption rate constant. The area under the concentration–time curves (AUC) were calculated by the trapezoidal rule[13] and further extrapolated to infinity by dividing the last experimental concentration by the terminal slope (λz). Statistical moment theory was applied to calculate the mean residence time (MRT) for IVM as follows:

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}$$

where AUC is as defined previously and AUMC is the area under the curve of the product of time and drug concentration versus time from zero to infinity.[13] A normality test was performed for testing if the data were sampled from populations that follow Gaussian distributions. This assumption was tested using the Kolmogorov and Smirnov method. Mean pharmacokinetic parameters for IVM obtained after its administration to both elephant groups were statistically compared using Student's t-test. The assumption that the data obtained after both treatments have the same variance was assessed. A nonparametric Mann-Whitney test was used where significant differences among standard deviations were observed. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The methodology used to quantify IVM in plasma was validated following well-established analytic standards. The linear regression lines showed $r \geq 0.998$. The mean recoveries of IVM from plasma were >70%. The interassay precision of the analytic procedures obtained after HPLC analysis of IVM-spiked standards showed a CV <20%. The limit of quantification was established at 0.1 ng/ml for plasma and 1 ng/g for feces.

Ivermectin was detectable in plasma up to 12 day posttreatment. There was no statistically significant difference detected in plasma or fecal IVM concentrations for full-ration versus restricted-ration groups. The plasma and fecal IVM concentration profiles obtained for both groups are summarized in Figures 1 and 2. The main pharmacokinetic parameters for IVM in plasma and feces are summarized in Tables 1 and 2. The C_{MAX} in feces were between 264–311-fold higher than those obtained in plasma. A rapid fecal elimination and fecal T_{MAX} (1.17 day) were observed. Fecal IVM concentrations were nearly undetectable at 7 day postadministration.

Table 1. Plasma pharmacokinetic parameters (mean ± SD) for ivermectin following its oral administration to fed and fasted African elephants (0.1 mg/kg).

Kinetic parameters	Fed	Fasted
Absorption half-life (day)	0.11 ± 0.04	0.16 ± 0.06
Time to maximum plasma concentration (day)	0.32 ± 0.11	0.34 ± 0.10
Maximum plasma concentration (ng/ml)	5.91 ± 3.37	8.49 ± 6.33
Area under the concentration-versus-time curve (ng × day/ml)	17.2 ± 14.5	20.3 ± 15.9
Mean residence time (day)	3.14 ± 1.36	2.85 ± 0.89
Elimination half-life (day)	4.47 ± 2.03	3.12 ± 1.13

DISCUSSION

Time-related pharmacokinetic variables in elephants are similar to those reported in horses, including a short T_{MAX}, demonstrating rapid absorption.[32] The high fecal IVM levels found within 24 hr of administration, along with a dramatically higher fecal versus plasma AUC and longer fecal versus plasma $T_{1/2}$ suggest that most of the drug is eliminated in the feces without systemic absorption. Similar findings after oral administration in horses show that nearly 90% of the total drug is excreted in feces at 4 day posttreatment.[31] Maximum plasma concentrations, however, are substantially lower than values reported following 0.2 mg/kg p.o. dosaging in horses[32] and sheep.[28] These findings suggest that the dosage of 0.1 mg/kg p.o. is insufficient, as compared with efficacious doses in other species, and may explain the poor efficacy against lice observed after its oral administration at a dosage of 0.1 mg/kg in elephants.[38]

Ivermectin is administered by several different routes, including subcutaneous, intramuscular, oral, intraruminal, and topical. The oral route of administration was chosen for this study because it is noninvasive and effective, and has been recommended anecdotally in elephants. Furthermore, there are reports of pain associated with i.m. IVM injections in elephants[17] and of inflammation and tissue necrosis following s.c. injection in horses.[5] However, both oral and topical routes of IVM administration are associated with decreased bioavailability,[2,32] lower plasma IVM concentrations,[3,15,31,34] and shorter duration of activity[7,20,25,30] as compared to parenteral treatment in both ruminants and equids. For elimination of lice in particular, the s.c. route of IVM for treatment of lice on cattle is more effective than a 2×dose administered orally. Interestingly, the oral route is at least as clinically efficacious against gastrointestinal parasites as is the s.c. route.[7,20,29] This is the case because the drug level in the gastrointestinal tract is likely to be quite high immediately following oral administration and seems to exert a transient, local effect on parasites.[39] Although degradation of IVM[1] and doramectin[14] in the ruminant gastrointestinal tract has not been ruled out, a high degree drug stability has been reported in both sheep ruminal content and abomasal content.[21,24]

Suggested causes for the disparity in IVM bioavailability following different administration routes include adsorption of orally administered IVM to digesta, as demonstrated in sheep,[1,21,24] and activity of a transport protein at the intestinal lining of the small intestine.[6] These findings are further supported by demonstration that higher versus lower feed volume in association with oral IVM administration results in decreased drug bioavaliability in sheep.[1,40] Similarly, the closely related drug moxidectin has reduced bioavailability when administered orally to fed verses fasted horses.[3] Theoretically, the phenomenon of particulate binding could have even greater implications in the elephant, given the comparatively vast digestive tract. Therefore, feed restriction was evaluated in this

Table 2. Fecal pharmacokinetic parameters (mean ± SD) for ivermectin following its oral administration to fed and fasted African elephants (0.1 mg/kg).

Kinetic parameters	Fed	Fasted
Time to maximum plasma concentration (day)	1.17 ± 0.41	1.17 ± 0.41
Maximum plasma concentration (ng/ml)	1,291 ± 479	1,257 ± 770
Area under the concentration-versus-time curve (ng × day/ml)	1,734 ± 569	1,627 ± 380
Mean residence time (day)	1.37 ± 0.21	1.41 ± 0.33
Elimination half-life (day)	0.83 ± 0.34	1.15 ± 0.43

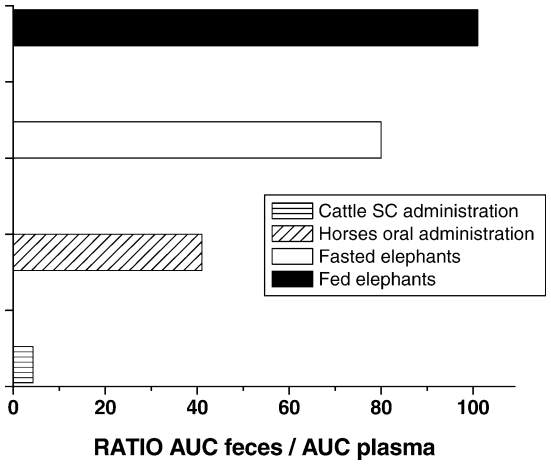

Figure 3. Comparative ratio between the area under the concentration-versus-time curve obtained for ivermectin in feces and plasma in fed and fasted elephants. The data from horses and cattle were adapted from Perez et al.[30,31] and Lifschitz et al.[23,] respectively.

study as a strategy to increase gastrointestinal IVM absorption in elephants. Although the difference in the two groups was not statistically significant, the small sample size must be taken into consideration for all variables. The ratio between mean AUC_{feces} and AUC_{plasma} was slightly higher in the fed animals (100) compared to that obtained in fasted elephants (80), indicating a potential effect of food restriction on the absorption of IVM that may warrant further investigation. Figure 3 shows the comparative ratio between AUC_{feces} and AUC_{plasma} obtained in elephants and horses following oral administration, and in cattle following s.c. administration. The relatively high ratio in elephants supports the theory that less orally administered drug is absorbed in elephants, possibly because of the large gastrointestinal tract volume and an increased opportunity for binding to particulate matter. For practical purposes, it appears that dietary restriction is not an effective means of increasing IVM absorption in elephants.

Increasing attention has been given to the potential for environmental contamination and impacts on important local fauna such as dung beetles, in association with ivermectin.[11,27] Given the high fecal volume and IVM concentration in elephants, the potential for environmental impact should be considered in situations where such organisms may be affected. The measurements of fecal elimination in elephants provide a basis to generate protocols for fecal removal, where applicable. Based on the rapid fecal T_{MAX} and $T_{1/2}$ following oral administration of IVM to elephants (Table 2), efforts to remove contaminated feces could soundly be focused over the first 48 hr. Based on the lack of detectable fecal concentrations beyond day 7, minimal environmental contamination may be anticipated beyond that time.

Although IVM may be effective for treating some infections in elephants at a dosage of 0.1 mg/kg, this dosage results in low plasma concentrations due to rapid fecal excretion of unabsorbed drug. Target parasites and tissues must be considered when choosing a dose. The required tissue levels of IVM for elimination of different parasites varies with factors such as parasite location, type, and degree of anthelmintic resistance.[19,24] Dietary restriction appears to be an impractical means of increasing IVM absorption in elephants. Administration of 0.2–0.4 mg/kg orally to elephants should prove more clinically effective at eliminating both internal and external parasites, and may minimize development of parasite resistance. The higher dose range should be utilized for treating external parasites as compared to gastrointestinal parasites, which are more readily eliminated by the oral route. Further investigation into the topical route of administration and clinical efficacy could be useful.

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