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Dosage Requirements of Orally Administered Ibuprofen in African and Asian Elephants (Last Updated: 3-Dec-2002)

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Introduction

Musculoskeletal disorders due to trauma and arthritis occur commonly in captive elephants, affecting 73% of the animals studied in 69 zoos in North America [1]. To treat these and other conditions, non-steroidal anti-inflammatory agents are used strictly on an empirical basis in elephants without knowledge regarding dosing, efficacy or toxicity. Physiologic diversity and the large body size of elephants, compared to other species, make dosages based on metabolic scaling calculations unreliable [2-5]. Ibuprofen is one of the most popular drugs used for the treatment of inflammatory conditions in captive elephants, and empirical dosages of ibuprofen administered to captive elephants range between 0.5 - 4.0 mg/kg with a median dosing frequency of 24 hours [2]. Seven mg/kg is the average dose given to humans, and therapeutic serum concentrations range between 15 and 30 mg/L [6]. No pharmacokinetic research has been conducted on the use of non-steroidal anti-inflammatory agents in elephants. Determination of safe and therapeutic dosing regimens for ibuprofen that account for potential differences based on species and sex in drug metabolism will improve medical management of captive elephants by providing:

1. Efficacious dosage regimens,
2. Improved control of pain, and
3. Prevention of potential toxic side effects resulting from improper drug administration.

Evidence suggests that there are species differences in drug metabolism between African and Asian elephants [2,3] and variations in drug metabolism have been documented in other animals based on gender [7]. Differences in pharmacokinetic parameters for various drugs between elephant species have been demonstrated for both antibiotic (e.g., trimethoprim-sulfamethozazole [3]) and anesthetic agents (e.g., ketamine HCl, whereby over three times the dose of ketamine is required for immobilization of African as compared to Asian elephants [8]).

The purpose of this study was to

1. Determine the pharmacokinetic parameters of ibuprofen administered per os in elephants,
2. Ensure that effective serum concentrations of the drug were maintained for sufficient periods of time, and
3. Compare ibuprofen serum concentrations between the two species of elephant as well as between males and females. These data were used to design a therapeutic dosing regimen that maintains ibuprofen concentrations at or slightly above levels known to be efficacious in other species for treatment of musculoskeletal disorders and other inflammatory conditions.

Materials and Methods

Twenty healthy elephants (five males and five females of each species) housed in zoos throughout North America were used in this study. Pilot studies were conducted at the Oregon Zoo with Asian elephants using empirically derived dosing regimens and preceded each set of clinical trials to ensure that proper ranges for dosage and dosing frequency determinations would be utilized. Based on pilot study results, the best therapeutic dose for ibuprofen was determined by using 4, 5 and 6 mg/kg dosages in each animal. Weights were obtained prior to initiation of the study, and ibuprofen was given orally with food treats like apples or bread. Blood samples were taken from superficial ear veins and were collected at -5, 15, 30, 45, 60 min, 1.5, 2, 4, 10, 12, 24 and 48 hr post-administration from all elephants. Wash-out periods between trials were 3 wks in duration and allowed for complete elimination of residual drug metabolites.

The optimal dosing frequency was then determined by examining two different dosing intervals (12 and 24 hr) utilizing the therapeutic dosage. Blood samples were collected hourly for 4 hrs after each of three administrations, then every 6 hrs plus 1 hr prior to the next administration. A 3 wk wash-out period was included between these two trials.

Serum ibuprofen concentrations were quantified by high-performance liquid chromatography (HPLC) after sample preparation. Pharmacokinetic data analysis was modeled and fitted using the software program Win NONLIN (1997, version 1.5), and both compartmental and non-compartmental analyses are being performed. Estimates predicting appropriate doses and dosing intervals for ibuprofen were based on literature values of identified therapeutic serum concentrations [9].

Preliminary Results

Following administration of 4 mg/kg ibuprofen and a rapid absorption phase, mean ibuprofen serum concentrations peaked in African and Asian elephants at 4 hrs at 16.75 $\pm$ 6.79 μg/ml (mean$\pm$ SD). Five mg/kg dosages of ibuprofen resulted in peak serum concentrations of 17.20 $\pm$ 7.78 μg/ml, and with 6 mg/kg dosages, serum concentrations increased to 22.42 $\pm$ 12.30 μg/ml. Ibuprofen was eliminated with first-order kinetics characteristic of a single-compartment model with a half-life of 4 to 4.5 hrs. The volume of distribution (Vd/F) was estimated to be 200.8 $\pm$ 101.17 ml/kg for African and 164.4 $\pm$ 34.60 ml/kg for Asian elephants. The doses used in this study with elephants resulted in serum concentrations at or above therapeutic levels (15 - 30 mg/L) for up to 12 hrs. Serum ibuprofen concentrations decreased to below 5 μg/ml 24 hr post-administration in all elephants.

There were no statistically significant pharmacokinetic parameter differences between males and females of either species; however, differences between African and Asian elephants did occur. The mean AUC and t1/2 life values for Asian elephants were higher as compared to African elephants, and the mean clearance and elimination rate constant were lower in Asian elephants as compared to African elephants. Asian elephants required approximately 1 mg/kg less ibuprofen as compared to African elephants to achieve therapeutic serum concentrations. Ibuprofen administered at 6 mg/kg/12 hrs for Asian elephants and at 7 mg/kg/12 hrs for African elephants resulted in therapeutic serum concentrations of this anti-inflammatory agent.

Conclusions

Ibuprofen appears to follow linear pharmacokinetics. Differences in kinetic parameters between sexes were not statistically significant, but a larger sample size (e.g., n=10) would provide more reliable data. Therapeutic dosage regimens for ibuprofen appear to be 7 mg/kg given every 12 hours for African elephants and 6 mg/kg for Asian elephants, also given every 12 hours.

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