PHARMACOKINETICS OF ORALLY ADMINISTERED IBUPROFEN IN ELEPHANTS

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Abstract

Musculoskeletal disorders (e.g., trauma, 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, nonsteroidal anti-inflammatory agents (e.g., ibuprofen and phenylbutazone) are used strictly on an empirical basis in elephants. There is some indication that species differences in drug metabolism exist between African (*Loxodonta africana*) and Asian (*Elephas maximus*) elephants, although this has not been substantiated.[2] Determination of safe and therapeutic dosing regimens for ibuprofen and phenylbutazone will improve medical management of captive elephants by providing efficacious dosage regimens, improved control of pain, and prevention of potential toxic side effects resulting from improper drug administration.

The purpose of this study was to: 1) determine the pharmacokinetic parameters of ibuprofen administered per os in elephants, and 2) establish therapeutic dosage regimens for African (*Loxodonta africana*) and Asian (*Elephas maximus*) male and female elephants. 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. Therapeutic dosage requirements were determined using 4, 5 and 6 mg/kg dosages in each animal, and blood samples were collected at –5, 15, 30, 45, 60 min, 1.5, 2, 4, 10, 12, 24 and 48 hr post-oral administration from superficial ear veins. Optimal dosing frequency was then determined by conducting 12- and 24-hr dosing interval trials, with blood samples collected hourly for 4 hr after each of three administrations, then every 6 hr plus 1 hr prior to the next administration. Washout periods between all trials were 3 wk in duration and allowed for complete elimination of residual drug metabolites.

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

elephants. There were no statistically significant pharmacokinetic parameter differences between males and females of either species, and differences between African and Asian elephants existed but were not significant ($P < 0.12$). The mean AUC and $t_{1/2}$ 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. Ibuprofen administered at 6 mg/kg/12 hr for Asian elephants and at 7 mg/kg/12 hr for African elephants resulted in therapeutic serum concentrations of this anti-inflammatory agent.

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