Clinical Interpretation of Pharmacokinetic and Pharmacodynamic Data in Zoologic Companion Animal Species

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• Analgesia • Efficacy • Potency • Half-life • Clearance
• Volume of distribution

The treatment and prevention of pain in zoologic companion animals is difficult because of the lack of data available on the safety and efficacy of drugs. The ideal situation for determining effective drug dosages is with controlled clinical trials, however these are rarely performed in veterinary species because of the high costs of the studies, number of animals needed, and difficulty in working with many of these species. Many dosage recommendations are based on perceived response to therapy, clinical experience, and lack of observable toxicity. However, these extrapolations are difficult to interpret for several reasons. The behavior of companion exotic animals often results in these animals hiding behaviors associated with disease or pain in order to minimize identification as weakened animals by predators or other animals within the herd, pack, or other social group. Therefore signs that are easy to observe in domesticated companion animals, such as lameness in dogs, are difficult to observe in nondomesticated animal species even with a trained and experienced observer.

For example, an animal may seem better after administration of an analgesic, but the pain may not have truly been controlled and the response may be caused by the animal trying to mask the signs in the presence of the observer, by healing of the injury, or by normal variations in pain intensity. The clinical observation in this case would be a perceived improvement after analgesic administration when an improvement did not truly occur. The same treatment is then administered to a similar animal a month later and the same scenario occurs: a perceived improvement when

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an improvement did not occur. The clinician now has some confidence that the treatment worked, despite the low number of animals treated, but in reality the analgesic did not work. The clinician then passes the treatment information to another colleague who uses the information with the same perceived improvement when none occurred. The information has then been independently verified and makes its way onto a listserve or by word of mouth at meetings or symposiums to other clinicians and eventually into a formulary. The formulary then undergoes several editions over the years, is referenced by other sources, and the incorrect dosing information becomes dogma. Through nobody's fault, and primarily because of the lack of available objective data, incorrect dosing information can easily become dogma, and this has occurred in veterinary medicine in all species, domesticated and nondomesticated.

The previous scenario emphasizes the importance of objective data and the need for controlled studies in animals. The lack of objective data in zoologic companion animals has numerous causes including the lack of funding, difficulty in handling some animal species, increased animal stress, lack of available animal numbers, the rarity and value of certain species, and the potential for adverse effects. However, without adequate data, therapeutic decisions are difficult to make, especially when treating the large number of animal species, including amphibians, reptiles, birds, and exotic small mammals.

STUDY DESIGNS EVALUATING A THERAPEUTIC AGENT

A logical progression in evaluating a therapeutic agent such as an analgesic would include pharmacokinetic (PK) studies, followed by pharmacodynamic (PD) studies or integrated PK-PD studies, and eventually controlled clinical trials. PK studies evaluate the changes in plasma concentrations over time, the relationship between plasma concentrations and dose, the effects of different routes of administration on the plasma concentrations, and the potential for extrapolating plasma concentrations within a dose range. The effect the drug elicits is not a primary outcome of PK studies. PD studies evaluate the effect produced by the drug after it is administered. PD studies may evaluate a single dose rate or evaluate escalating doses. PK-PD studies integrate changes in drug concentrations versus changes in the effect (ie, whether an increase in dose, or plasma concentration, results in an increase in analgesia). Once a targeted dose is chosen based on PD, or preferably PK-PD, studies, the dose regimen should be evaluated in a controlled clinical trial to confirm that the experimental model accurately predicts the desired effect and lack of adverse effects in clinical patients.

Controlled clinical trials evaluate the test drug in patients clinically affected with an injury or disease, for example, evaluation of a nonsteroidal antiinflammatory drug (NSAID) in ducks with lameness associated with synovitis. In a positive controlled trial, the drug to be tested is compared with a drug known to elicit the desirable effect. For example, a positive controlled trial could include oral meloxicam as the test drug and flunixin as the positive control for the treatment of lameness associated with synovitis. In vivo studies have shown that flunixin inhibits plasma thromboxane for 6 to 12 hours in mallard ducks.[1] Some assumptions in positive controlled trials include that previous studies have shown that the positive control is effective in the species to be tested, the positive control is effective at the administered dosage, the duration of effect of the positive control has been determined, and the positive control is effective for the specified disease. However, there are few clinical studies in nondomestic species that meet these assumptions. Limitations of the lame duck example are: flunixin has not been shown to produce analgesic effects in ducks or in ducks with synovitis; the dose of flunixin was determined in an experimental model (inhibition of plasma thromboxane)