Feline Drug Metabolism and Disposition

Pharmacokinetic Evidence for Species Differences and Molecular Mechanisms

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KEYWORDS

• Cat • Species differences • Glucuronidation • Pharmacokinetics

KEY POINTS

- Acetaminophen, propofol, carprofen, and aspirin are eliminated more slowly in cats, and are all metabolized by conjugation.
- Cats lack uridine diphosphate glucuronosyltransferase (UGT) 1A6 and UGT1A9, which glucuronidate acetaminophen and propofol, respectively.
- Slower aspirin clearance results mainly from deficient glycine conjugation and not deficient glucuronidation.
- Cats lack *N*-acetyltransferase 2, which may be the reason they are prone to developing methemoglobinemia rather than hepatotoxicity from acetaminophen.
- Cats have low thiopurine methyltransferase activity, which causes sensitivity to azathioprine toxicity.
- Piroxicam is eliminated more quickly in cats than in humans and dogs, but the reason for this is unknown.

INTRODUCTION

Veterinarians are well aware that cats are not simply small dogs with regard to their physiology and pharmacology. However, there are few articles that have critically evaluated the evidence for such species differences and their resultant impact on drug efficacy and toxicity in cats. In this article, the primary literature is reviewed, focusing on the available evidence for differences in drug metabolism and disposition between cats, dogs, and humans, as well as the molecular and genetic mechanisms that may explain these differences.

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DRUG PHARMACOKINETIC DIFFERENCES BETWEEN CATS, DOGS, AND HUMANS

Fig. 1 shows the results of a preliminary survey of the current literature comparing elimination half-life values for 25 different drugs in cats, dogs, and humans. The drugs were chosen to represent a variety of drug elimination mechanisms, including conjugation (n = 8), oxidation (n = 9), and excretion of unchanged drug into the urine and/or bile (n = 8).

Several trends are apparent in **Fig. 1**:

- All of the drugs that are eliminated more slowly in cats (ie, aspirin, propofol, acetaminophen, and carprofen) are cleared by metabolic conjugation, including glucuronidation, sulfation, and/or glycination.
- Piroxicam, which is metabolized mainly by oxidation, is eliminated more rapidly in cats compared with dogs and humans (ie, the opposite of the conjugated drugs).
- Elimination half-life values were highly correlated between dogs and cats for the nonmetabolized drugs, and poorly correlated for the metabolized (oxidized and/or conjugated) drugs.
- Human elimination half-life data were poorly predictive of dog and cat elimination half-life data for most of the drugs evaluated.

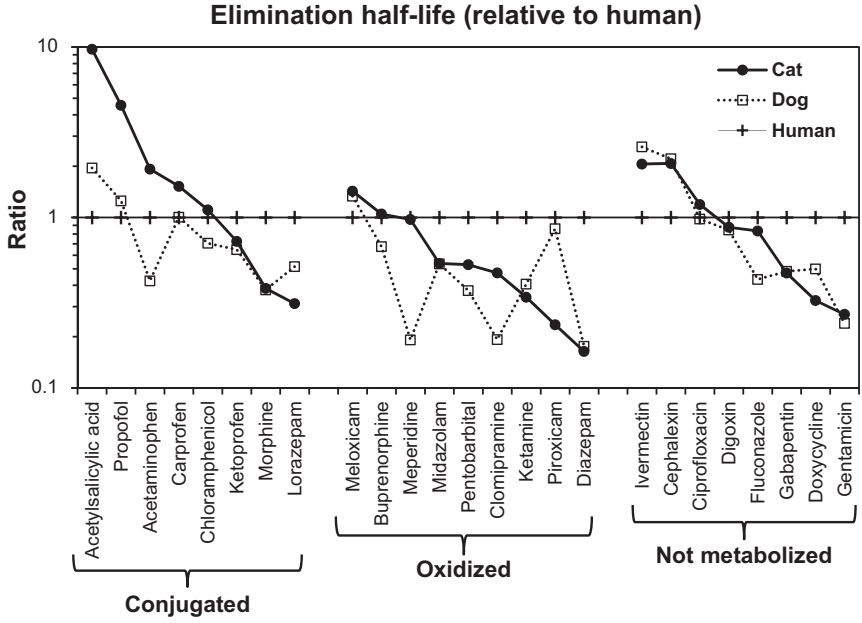

Fig. 1. Pharmacokinetic evidence for differences in drug elimination rates between cats, dogs, and humans. Shown is a comparison of published elimination half-life values in cats (*filled circles*), dogs (*open squares*), and humans (*plus symbols*) for representative drugs that are primarily eliminated by conjugation (glucuronidation, sulfation, and glycination) or oxidation (cytochrome P450 [CYP] enzymes), or that are excreted primarily unchanged into urine and/or bile. All values are expressed as a ratio of the human value. Complete pharmacokinetic data and literature references are given in **Table 1** for acetylsalicylic acid, propofol, acetaminophen, carprofen, and piroxicam. Because of space limitations, the references giving data for other drugs are available directly from the author.