Feline Drug Metabolism and Disposition
Pharmacokinetic Evidence for Species Differences and Molecular Mechanisms

Michael H. Court, BVSc, PhD

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.](image-url)
Table 1 lists the elimination half-life, plasma clearance (CL), and volume of distribution (Vd) values of those drugs from Fig. 1 that had longer (n = 4) or shorter (n = 1) elimination half-life values in cats compared with dogs and humans. The likely mechanisms for these species differences and their implications for drug use in the cat are discussed later.

Acetylsalicylic Acid (Aspirin) and Salicylates

Aspirin is used in cats for acute pain and inflammation or more chronically as an antithrombotic. However, because of slow elimination of aspirin relative to dogs, the recommended doses are 2 to 4 times lower and the dose frequencies are 4 to 6 times longer in cats.16 Although slow elimination of aspirin in cats has frequently been attributed to deficient glucuronidation,16 a review of the available literature on aspirin metabolism suggests that other causes are more likely responsible.

After ingestion, aspirin is normally rapidly converted to the major circulating active metabolite, salicylic acid. Salicylic acid is then excreted in the urine unchanged, or following conjugation with glucuronic acid (forming phenolic and acyl glucuronides) or with glycine (forming salicylurate).17 However, as shown in Fig. 2, there is considerable variation in use of these pathways between species. After a therapeutic dose of aspirin (650 mg orally), humans excrete primarily salicylurate (69%), and salicylurate glucuronide (10%), with some salicyl glucuronides (12%) and unchanged salicylate (8%).17 In comparison, dogs excrete approximately equal amounts of unchanged salicylate, salicylurate, and salicyl glucuronides into their urine after administration of a

<table>
<thead>
<tr>
<th>Drug</th>
<th>Species</th>
<th>Half-life (h)</th>
<th>CL (mL/min/kg)</th>
<th>Vd (L/kg)</th>
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<tr>
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<td>2.9</td>
<td>1.3</td>
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<tr>
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<td>13</td>
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<td></td>
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<td></td>
<td>Humanb</td>
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<td>0.050</td>
<td>0.16</td>
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</tbody>
</table>

Abbreviations: CL, plasma clearance; F, bioavailability; Vd, volume of distribution.

aData for disposition of the active metabolite, salicylic acid.

bOral dosing data provided because intravenous or other parental administration data are not available. CL is therefore CL/F and Vd is Vd/F. However, bioavailability for these drugs is considered to be high.

Data from Refs.1-15
44 mg/kg intravenous (IV) dose of sodium salicylate. In the same study, cats excreted mostly salicyl glucuronides (60%–80%) with some unchanged salicylate (12%–23%) but only a minor amount of salicylurate (5%).

These data suggest that cats can readily glucuronidate salicylic acid, although the type of glucuronide formed is unclear (phenolic and acyl glucuronides are possible). This possibility is supported by in vitro studies that showed significant glucuronidation of salicylic acid by liver tissue slices from cats. In contrast, the urinary metabolite data (see Fig. 2) indicate that cats are deficient in the conjugation of salicylate with glycine to form salicylurate. Although little is known about the enzyme process that mediates salicylic acid glycination, available evidence suggests that it is a 2-step process involving activation of salicylic acid with coenzyme A (Co-A) to form a salicyl-CoA thioester, followed by conjugation with the amino group of glycine to form an amide-linked glycine conjugate. Enzymes thought to be involved in this process in humans include acyl-CoA synthetase medium-chain 2B (ACSM2B, also called HXM-A), and glycine N-acyltransferase (hGLYAT), respectively. Both enzymes are localized to the mitochondrial matrix of liver and kidney tissues. A complementary DNA encoding a feline ortholog of hGLYAT was recently identified (GenBank accession number JV729374), whereas a feline ACSM2B ortholog has yet to be reported.

Slower elimination in cats might be expected for salicylate drugs other than sodium salicylate and aspirin, such as methylsalicylate (oil of wintergreen; Bengay) and trolamine salicylate (Aspercreme), although there is no direct evidence for this in the literature.

**Acetaminophen**

Although acetaminophen is one of the most widely used nonprescription treatments for mild pain and fever in humans, this drug is rarely used in dogs, and is

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**Fig. 2.** Cats can readily glucuronidate salicylate, but they poorly conjugate salicylate with glycine (forming salicylurate). Shown are data from several studies comparing the urinary metabolites of salicylate when administered as the sodium salt to 7 dogs and 2 cats (1 male, 1 female) at 44 mg/kg intravenously, or orally as acetylsalicylic acid to 25 human volunteers at a therapeutic dose of 650 mg, or to 24 human patients who had intentionally taken a moderate aspirin overdose. (Data from Refs and Patel DK, Hesse A, Ogunbona A, et al. Metabolism of aspirin after therapeutic and toxic doses. Hum Exp Toxicol 1990;9(3):131–6.)
contraindicated for use in cats. One of the reasons is that dogs, and especially cats, show significant methemoglobinemia and other signs of oxidative injury to erythrocytes (Heinz bodies and anemia) following acetaminophen doses that would be considered nontoxic to humans and other species.\textsuperscript{5,24}

In humans, acetaminophen toxicity with increasing doses is typically manifested as acute hepatocellular injury that can proceed to liver failure if not appropriately treated.\textsuperscript{25} The mechanism of acetaminophen hepatotoxicity is a consequence of saturation of the major conjugative metabolic pathways (glucuronidation and sulfation) and increased metabolism of acetaminophen by cytochrome P450 (CYP) in liver to form a highly reactive metabolite \textit{N}-acetyl-\textit{p}-quinone-imine (NAPQI) (\textit{Fig. 3}).\textsuperscript{26} NAPQI is normally detoxified by glutathione conjugation, but once glutathione supplies are depleted (following overdose), NAPQI causes cellular damage. Acetaminophen hepatotoxicity is normally treated by administering the glutathione precursor \textit{N}-acetylcysteine.

Several explanations for acetaminophen sensitivity in cats have been proposed, including their hemoglobin, which may be more sensitive to oxidative injury, as well as a lower antioxidant capacity of their erythrocytes.\textsuperscript{27} However, these explanations do not account for the sensitivity of dogs to methemoglobinemia. Also, NAPQI

\textbf{Fig. 3.} Proposed mechanisms for species differences in acetaminophen toxicity. Acetaminophen overdose in humans (and most other species) results in acute hepatotoxicity. The mechanism involves saturation of the detoxifying conjugation pathways (sulfation, glucuronidation, and glutathione conjugation), resulting in accumulation of the oxidative reactive metabolite NAPQI in the liver with resultant cellular damage. However, in cats and dogs, acetaminophen toxicity primarily manifests as methemoglobinemia with Heinz body anemia. McConkey and colleagues\textsuperscript{27} (2009) proposed the existence of a futile cycle in erythrocytes that involves deacetylation of acetaminophen to \textit{p}-aminophenol by carboxyesterases (CES) and then reacetylation of \textit{p}-aminophenol back to acetaminophen by \textit{N}-acetyltransferase (NAT) isoform 2. \textit{p}-Aminophenol is a reactive compound that can co-oxidate with hemoglobin to form methemoglobin. Although methemoglobin can be reduced back to hemoglobin by nicotinamide adenine dinucleotide, reduced form, cytochrome b5 reductase, this capacity is limited. \textit{p}-Aminophenol is proposed to accumulate in cat and dog erythrocytes (and not in humans erythrocytes) because both cat and dog (unlike humans and most other species) lack NAT2. Cats may be more susceptible than dogs to this toxicity because they also lack several uridine diphosphate glucuronosyltransferases (UGTs), including UGT1A6 and UGT1A9, which are essential for efficient elimination of acetaminophen by glucuronidation. Acetaminophen clearance is lower in cats, resulting in increased levels of acetaminophen (and probably \textit{p}-aminophenol).
is formed by CYPs primarily in the liver and not in the blood. Given the reactivity of this compound, it is unlikely that NAPQI could reach significant levels in erythrocytes. An alternate hypothesis has been explored by McConkey and colleagues\textsuperscript{27} (2009), as shown in Fig. 3. They propose the existence of a futile cycle in erythrocytes that involves deacetylation of acetaminophen to \textit{p}-aminophenol by carboxyesterases (CES) and then reacetylation of \textit{p}-aminophenol back to acetaminophen by \textit{N}-acetyltransferase (NAT) isoform 2. \textit{p}-Aminophenol is known to be a reactive compound that can co-oxidate with hemoglobin to form methemoglobin. Although methemoglobin can be reduced back to hemoglobin by nicotinamide adenine dinucleotide, reduced form, cytochrome b5 reductase, this capacity is limited. \textit{p}-Aminophenol is proposed to accumulate in cat and dog erythrocytes (and not in human erythrocytes) because both cat and dog (unlike humans and most other species) lack NAT2.

Cats may be more susceptible than dogs to acetaminophen toxicity because they also lack several uridine diphosphate glucuronosyltransferases (UGTs), including UGT1A6 and UGT1A9, which are essential for efficient elimination of acetaminophen by glucuronidation (discussed further later).\textsuperscript{28} In support of this, acetaminophen glucuronidation by cat liver microsomes is slow\textsuperscript{29} and acetaminophen glucuronide is a minor metabolite of acetaminophen in cat urine, whereas it is the main metabolite in dogs and humans (Fig. 4).\textsuperscript{5,30,31} As a result, acetaminophen clearance is lower, and

![Fig. 4. Cats are sensitive to the toxic effects of acetaminophen, in part because they glucuronidate acetaminophen less efficiently than humans or dogs. Shown are data from several studies comparing the urinary metabolite profiles of acetaminophen following oral administration of a nontoxic dose of 100 mg/kg to 4 dogs, a toxic dose of 120 mg/kg to 6 cats, a therapeutic dose of 20 mg/kg to healthy human volunteers, and an intentional overdose taken by human patients. (Data from Savides MC, Oehme FW, Nash SL, et al. The toxicity and biotransformation of single doses of acetaminophen in dogs and cats. Toxicol Appl Pharmacol 1984;74(1):26–34, for cat and dog; and Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmacol 1980;10 Suppl 2:291S–85, for human volunteers and overdose patients.)](#)
half-life is longer, in cats (see Table 1), resulting in increased circulating levels of acetaminophen, and probably higher p-aminophenol levels in blood.

**Propofol**

Propofol administered intravenously is commonly used for induction and short-duration anesthesia in dogs and humans. However, repeated dosing or the use of continuous infusions of propofol in cats has been associated with prolonged anesthetic recoveries. Furthermore, repeated daily dosing of propofol results in oxidative injury to erythrocytes and increased Heinz body formation after 3 days, and more severe symptoms including malaise, anorexia, and diarrhea after 5 days. A recent study suggested that increasing the dosing interval to 48 hours may ameliorate the more severe symptoms, although there was still evidence for significant Heinz body formation following the first dose.

A toxicity syndrome (called propofol infusion syndrome [PRIS]) in human patients has been associated with administration of high doses of propofol by infusion for up to 48 hours in the intensive care setting. The most frequent symptoms include metabolic acidosis, bradyarrhythmias, and progressive myocardial failure, with less frequent symptoms of rhabdomyolysis and renal failure. The mortality is about 80% in published cases, and 30% in cases reported directly to the US Food and Drug Administration. A recent study suggests that the incidence of PRIS is about 1.1% in patients admitted to an intensive care unit and receiving propofol for at least 24 hours, with an 18% mortality. The molecular mechanism underlying PRIS is currently unknown, although various studies have implicated inhibition of several mitochondrial proteins including carnitine palmitoyl-transferase I and the mitochondrial respiratory chain at complex II and IV, either directly by propofol, or by one of its metabolites. It is unknown whether interindividual differences in the metabolism of propofol can contribute to this syndrome.

Propofol is normally eliminated either by glucuronidation (directly) or by CYP-mediated oxidation to form 4-hydroxypropofol that is glucuronidated or sulfated and then excreted into the urine and the bile. The relative use of these pathways differs between species. In humans, about 60% of the dose is eliminated by direct glucuronidation (primarily by UGT1A9), whereas 40% is eliminated by oxidation (primarily by CYP2B6) followed by conjugation. However, in dogs, propofol is eliminated almost entirely by oxidation (primarily by CYP2B11) with only 2% of the dose eliminated by direct glucuronidation.

However, the metabolism of propofol in cats is unknown. Given that cats do not express an ortholog of UGT1A9, it might be speculated that propofol is mainly metabolized by alternate pathways including oxidation and sulfation. The slow clearance and prolonged elimination half-life of propofol in cats relative to humans and dogs (see Table 1) consequently might be explained by deficient glucuronidation in this species. The reason for oxidative injury to feline erythrocytes is less clear, although it might involve the same adverse mitochondrial effects of propofol (or a metabolite) that were proposed as the cause of PRIS in humans. In contrast, propofol is considered to have direct antioxidant effects and has been shown to protect against hemoglobin oxidation, although the antioxidant (or pro-oxidant) effects of its metabolites are unknown.

**Carprofen**

Carprofen is a nonsteroidal antiinflammatory drug that is commonly used for the treatment of mild to moderate acute and chronic pain in dogs. It is currently approved for use in cats by regulatory agencies in several countries (not the United States) for
postoperative analgesia given as a single dose of 4 mg/kg by injection.\textsuperscript{42,43} Although longer term use is discouraged because of a lack of safety data, it is also being used orally in cats for treatment of chronic pain.\textsuperscript{42} Carprofen was marketed for about 10 years for use in humans, but was withdrawn in 1995 for commercial reasons. The most common adverse side effects are gastrointestinal irritation and ulceration, which are more likely with prolonged use of the oral preparation. Available pharmaco-kinetic data (see Table 1) indicate that carprofen is cleared significantly more slowly in cats than in dogs and humans (by 2.8-fold to 4.8-fold) and has a 50% longer half-life. Lower doses and/or a longer dose interval consequently would likely need to be used in cats for chronic administration to achieve the same plasma drug levels as in dogs and humans.

Carprofen is cleared primarily by glucuronidation in the liver.\textsuperscript{44} No studies have been published that identify which human UGT glucuronidates carprofen. Slower elimination of carprofen in cats could be a consequence of deficient glucuronidation, although there is no direct evidence to support this. For example, it is not known whether cat liver microsomes glucuronidate carprofen more slowly than human or dog liver. Arguing against this contention is that several structurally related compounds, including pirprofen, flurbiprofen, and ibuprofen, are readily glucuronidated by cat liver microsomes.\textsuperscript{45} Carprofen is also highly bound to plasma proteins (<1% unbound in humans and dogs) and so pharmacokinetic differences might also be a consequence of species differences in protein binding, although such an analysis has not been reported.

**Piroxicam**

Piroxicam is a nonsteroidal antiinflammatory drug that was initially approved for use in humans as an antiinflammatory and analgesic, but has garnered a novel off-label use as a cancer chemotherapeutic in both human and veterinary medicine.\textsuperscript{13} Piroxicam pharmacokinetics are different in cats compared with dogs and humans (see Table 1). Relative to dogs and humans, cats show more than 10-fold higher clearance of piroxicam and a 3-fold to 4-fold faster elimination half-life. The mechanism for this difference is unclear.

In humans, about 50% of the dose is oxidized by CYP2C9 to 5'-hydroxypiroxicam\textsuperscript{46} and most of the remainder is hydrolyzed at the amide bond, presumably by an esterase. Resultant metabolites and some unchanged drug are excreted into urine and bile. 5'-Hydroxypiroxicam is also glucuronidated and excreted in the urine.\textsuperscript{47} There is no evidence for direct glucuronidation of piroxicam. Piroxicam (or possibly a metabolite) undergoes significant enterohepatic recirculation in people because pharmacokinetic studies have consistently shown secondary elimination peaks after administration, and a decrease in elimination half-life and faster clearance was observed in people coadministered the anionic sequestrant cholestyramine.\textsuperscript{15,48} Piroxicam is also highly bound (>99%) to human plasma proteins.\textsuperscript{49}

The excretory pathways in dogs are similar to those in humans except that an additional cyclodehydrated metabolite was identified representing as much as 12% of metabolites. Pharmacokinetic studies showing strong secondary elimination peaks also suggest that piroxicam undergoes significant enterohepatic recirculation in dogs.\textsuperscript{14} The metabolism and excretion of piroxicam in cats is unknown.

Several possibilities exist that might explain faster clearance of piroxicam in cats. Pharmacokinetic elimination profiles of piroxicam in cats do not show any evidence for enterohepatic recirculation (no secondary peaks).\textsuperscript{13} As a result, it is possible that the mechanism enabling recirculation in dogs and humans is deficient in cats, leading to faster clearance. An alternative is that cats might have a higher capacity for
clearance of piroxicam via hydroxylation or hydrolysis, or by elimination of unchanged drug. In addition, there may be lower plasma protein binding of piroxicam (and/or metabolites) in cats compared with dogs and humans that would tend to favor faster elimination.

**MOLECULAR BASIS FOR DIFFERENCES IN CATS VERSUS OTHER SPECIES**

Although an understudied area of research, over the last 20 years there has been considerable progress in understanding the molecular and genetic basis for differences in drug metabolism and disposition in cats compared with other species. Deficiencies in 4 different drug elimination pathways have been explored in detail, including glucuronidation (UGTs), acetylation (NATs), methylation (thiopurine methyltransferase [TPMT]), and active transport (ATP-binding cassette G2 [ABCG2]).

**Glucuronidation Deficiency**

Glucuronidation catalyzed by the UGT enzymes is an important metabolic process that transfers glucuronic acid to many different drugs, toxins, and endogenous compounds (such as steroids and bilirubin), thereby promoting efficient elimination into urine and/or bile. Humans express 19 different UGT isoforms that are classified based on genetic similarity into 2 families and 3 subfamilies (UGT1A, UGT2A, and UGT2B). UGT1A isoforms are encoded by a single gene that produces 9 different enzymes in humans by differential mRNA splicing (Fig. 5). Human UGT2A1 and UGT2A2 are also generated by splicing from a single gene, whereas UGT2A3 and all human UGT2B isoforms are products of separate genes. UGTs are primarily expressed in liver, kidney, and intestinal mucosa, which are the primary sites of drug metabolism.

Deficient glucuronidation is one of the oldest and most widely appreciated pharmacologic idiosyncrasies of cats (perhaps second only to so-called morphine mania). Reports regarding the inability of cats to glucuronidate drugs and toxins originated in the scientific literature nearly 60 years ago. Since then various studies have determined that this deficiency in cats is not generalized to all glucuronidated drugs, but depends on drug structure. The defect seems to mainly affect compounds with a simple planar phenolic structure.

Studies of UGT isoform substrate specificity in humans and other species indicate that simple planar phenolic compounds are mainly metabolized by several UGT1A isoforms expressed in liver, particularly UGT1A6 and UGT1A9. Furthermore, it has been shown that feline liver only expresses 2 different UGT1A isoforms, including UGT1A1 and UGT1A2, whereas humans express 5 different UGT1As in liver. UGT1A1 is likely to be conserved amongst species because it is essential for glucuronidating and clearing bilirubin. Although little is known about UGT1A2, it is most related to human UGT1A3 and UGT1A4, which glucuronidate drugs containing carboxylic acid and amines. No UGT1A isoform related to UGT1A6 or UGT1A9 was expressed in cat liver. The same study went on to identify the UGT1A6 gene by DNA sequencing but it contained multiple mutations in all cats. This finding suggests that a functional UGT1A6 gene had been present at one point in cats (or a cat species ancestor), but it had been permanently disabled in this species to form what is commonly called a pseudogene. As shown in Fig. 5, this finding was confirmed by the recent sequencing of the feline genome, which found only 2 isoforms (UGT1A1 and UGT1A2) and the UGT1A6 pseudogene. In comparison, based on available genome sequences, dogs express up to 10 different UGT1As, whereas humans express 9 different UGT1As (see Fig. 5).
Deficient glucuronidation of phenolic compounds has also been shown for other nondomestic felid species, including the African lion and caracal. This finding was confirmed by a recent molecular genetic study of a large number of carnivore species that showed UGT1A6 mutations in 17 different nondomestic felid species, representing all major felid lineages, including African lion, tiger, leopard, snow leopard, jaguar, Asiatic golden cat, African golden cat, serval, margay, Geoffrey’s cat, tigrina, Canada lynx, bobcat, puma (cougar), Florida panther, cheetah, and leopard cat. However, these mutations in UGT1A6 did not extend beyond the Felidae family to other Carnivora species, such as wolves, ferrets, bears, and raccoons, indicating that the first UGT1A6 mutation had evolved during the separation of the Felidae from other Carnivora species between 11 and 35 million years ago.

Fig. 5. Comparison of the size, structure, and exon content of the human, canine, and feline UGT1A genes. Each gene consists of multiple exons 1 (designated UGT1A1 to UGT1A11) each with their own promoter that are differentially spliced with the conserved exons 2 to 5. Exon 1 encodes for the UGT enzyme protein domain that binds to and determines substrate specificity, whereas the conserved exons code for the UDPGA-binding domain shared by all UGT1A enzymes. The human gene spans 180 kb and contains 9 functional exons 1 that encode 9 different UGT enzymes. The canine gene is smaller (130 kb) but includes 10 functional exons 1, encoding 10 different UGT enzymes. However, the feline UGT1A gene is smaller (only 40 kb) and has only 2 functional exons 1 that encode 2 different UGT enzymes. Also shown are 2 exons 1 in human and 1 exon 1 in cat that are considered pseudogenes (designated here by the suffix “p” added to the gene name) because they contain multiple mutations that prevent protein coding. UGT1A1 is conserved across all 3 species, probably because it encodes the only known enzyme capable of high-efficiency glucuronidation of bilirubin. (Data from Li C, Wu Q. Adaptive evolution of multiple-variable exons and structural diversity of drug-metabolizing enzymes. BMC Evolutionary Biology 2007;7:69 for human and dog genes, and from the University of California at Santa Cruz genome browser for the feline gene.)
In addition, although cats are deficient in several UGT1A enzymes, it is unknown whether other UGT isoforms are also different. In particular, it would be important to know whether cats express feline orthologs of human UGT2B7 and UGT2B15, which glucuronidate many different drugs. UGT2B7 selectively glucuronidates morphine in humans, and there is evidence for reduced morphine glucuronidation by cat liver.\textsuperscript{52} This contrasts with the pharmacokinetic data shown in Fig. 1 indicating that morphine is eliminated at a similar rate in dogs and even faster than in humans. It is possible that slow morphine glucuronidation in cats may be compensated by clearance through other pathways, including sulfation.\textsuperscript{57} UGT2B15 selectively glucuronidates lorazepam in humans, but this benzodiazepine seems to be glucuronidated readily in cats, suggesting that cats express a feline ortholog of human UGT2B15.\textsuperscript{58}

**Drugs with Evidence for Poor Glucuronidation in Cats**

Pharmacology texts and other sources frequently cite deficient glucuronidation as the cause of toxicity or need for dose reduction of glucuronidated drugs given to cats without adequate justification. For example, current evidence points to poor glycine conjugation (discussed earlier) rather than poor glucuronidation as the cause of slow aspirin clearance in cats.\textsuperscript{16} Box 1 lists drugs with clear evidence that they are glucuronidated either more slowly or with similar efficiency compared with other mammalian species. Evidence includes either comparative in vitro glucuronidation studies or in vivo metabolic studies.

Benzyl alcohol and benzoic acid are compounds that are frequently added to drugs as preservatives. Benzyl alcohol is metabolized to benzoic acid and then excreted as the glucuronide or glycine conjugate in most species. Cats are unable to glucuronidate benzoic acid, but can glycinate it, albeit slowly.\textsuperscript{63} Benzoic acid poisoning has been reported in cats and it has been recommended that the amounts of benzyl alcohol and benzoic acid used in pharmaceutical preparations for cats be minimized.\textsuperscript{64,65}

**NAT2 Deficiency**

N-Acetylation catalyzed by the N-acetyltransferase enzymes NAT1 and NAT2 is an important metabolic pathway in humans and most other species for several arylamine

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**Box 1**

**Drugs with direct evidence that they are glucuronidated more slowly (left column) or with similar efficiency (right column) in cats compared with other mammalian species**

<table>
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<tr>
<th>Drugs glucuronidated slowly in cats</th>
<th>Drugs glucuronidated efficiently in cats</th>
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</table>

*Data from Refs.\textsuperscript{18,29,45,52,53,57–62}
drugs including isoniazid, various sulfonamide antibiotics, dapsone, hydralazine, and procainamide. However, dogs (and all other canid species) lack this metabolic pathway because they lack both genes encoding these enzymes. Cats also lack NAT2, but express NAT1, albeit with lower enzyme activity compared with other species. NAT2 deficiency has been associated with low acetylation of sulfamethazine, sulfanilamide, sulfadimethoxine, and isoniazid by cat liver. It is not known whether dapsone and hydralazine are acetylated more slowly in cats. As mentioned earlier, the deficiency of NAT2 in cats, and of both NATs in dogs, are proposed to contribute to the mechanisms of toxicity of acetaminophen that are specific to these species.

TPMT Deficiency
Cats are highly susceptible to the adverse effects of azathioprine. This difference is most likely associated with the low TPMT activity that has been found in cat erythrocytes compared with several other species, including humans. S-Methylation by TPMT is an important detoxification mechanism for several drugs used for treatment of cancer (6-mercaptopurine) and for immunosuppression (azathioprine). The reason for the lower TPMT activity in cats is not known but could involve gene sequence differences (from other species) that affect enzyme level and/or enzyme affinity for substrate. Several polymorphisms in the coding sequence of the feline TPMT gene have been identified that affect enzyme protein levels and activity.

ABCG2 Deficiency
Fluoroquinolone antibiotic use has been associated with the development of temporary and permanent blindness in cats. A recent study suggests that this may be the result of inefficient efflux of fluoroquinolones by the ABCG2 transporter from the feline eye. A more complete discussion of this is provided by Mealey elsewhere in this issue.

SUMMARY
Cats are deficient in several drug conjugation pathways that can lead to slow elimination of certain drugs, and the need for dose adjustment or alternative therapies to avoid serious adverse effects. The most well-understood conjugation defect in cats causes reduced glucuronidation of phenolic drugs, such as acetaminophen and propofol. Cats lack UGT1A6 and UGT1A9, which glucuronidate these drugs in other species. Slower clearance of carprofen might also result from deficient glucuronidation, although direct evidence for this is lacking. However, slower aspirin clearance does not seem to result from deficient glucuronidation, and is more likely a consequence of poor glycine conjugation. Cats are also deficient in several other conjugation pathways, including N-acetylation by NAT2 and S-methylation by TPMT. NAT deficiency may be the reason cats (and dogs) are more prone to acetaminophen-induced methemoglobinemia rather than hepatotoxicity. TMPT deficiency likely results in sensitivity to azathioprine toxicity. No evidence was found for slower clearance of drugs that are eliminated by oxidation or unchanged into urine or bile. Piroxicam, an oxidized drug, was cleared more rapidly in cats than in humans and dogs, although the mechanism for this difference is unclear. Species differences in plasma protein binding might also explain observed differences in pharmacokinetics, especially for drugs that are highly bound. Much work is still needed to better understand the molecular causes of drug metabolism and disposition differences in cats, thereby enabling more rational prescribing of existing medications, and the development of more effective and safer drugs for this species.
REFERENCES


