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Drugs contraindicated in cat

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Abstract
While medicating cats, veterinarians have to very cautious else they can face serious adverse effects. Cats are different from other animals with respect to metabolism. Various drugs like antibiotics, Non-steroidal anti-inflammatory drugs (NSAIDs), anti-parasitic etc. are causing adverse effects in cats. The prescribed drugs may cause acute poisoning even at therapeutic doses. This review aims at providing information to clinical veterinarian, pet owner to be cautious while administering of drugs in cats. The adverse effects of contraindicated drugs are summarised here for accurate use of drugs and to avoid acute poisoning leading to death.

Keywords: cat, toxicity, glucuronidation

Introduction
Drugs are the modern world medicines for diseases that animals suffer from. While medicating cats, drugs are to be given only after being advised by veterinarians. As the cat is already suffering, care is to be taken to see that it further does not succumb to drug toxicity. As cats are lacking many drug conjugation pathways, they cannot metabolise certain drugs as other animals leading to slow metabolism and excretion of those drugs causing toxicities and other side effects. So, alternate therapeutic regimen or adjustment of dose of those drugs can be prescribed. The most accepted conjugation defect is reduced glucuronidation of phenolic drugs, such as acetaminophen and propofol. The drugs elimination mechanisms like conjugation, oxidation in cat vary from other animals like dogs and humans, and thus are excreted unchanged into the urine and/or bile. Drugs like aspirin, acetaminophen, propofol requiring metabolic conjugation, like glucuronidation, sulfation, glycination occur slower in cats. On the other hand piroxicam is eliminated more speedily in cats as it is metabolised by oxidation. This review aims to enlist all the drugs contraindicated in cats along with their side effects which can be of help to doctors, veterinarians as well as cat owners.

Mechanisms causing difference in metabolism in cats
Cats lack UDP-glucuronosyltransferase (UGT) enzymes like UGT1A6 and UGT1A9 responsible for glucuronidation of these drugs in other species. So, Slower carprofen clearance results from deficient glucuronidation and slower aspirin clearance occurs due to poor glycine conjugation. Cats are also deficient in N-acetyltransferase (NAT) enzymes specifically NAT2 which is responsible for N-acetylation conjugation pathways resulting in acetaminophen-induced methemoglobinemia. The deficiency of thiopurine methyltransferase (TPMT) responsible for S-methylation results in azathioprine toxicity. Drugs that are eliminated by oxidation have no changed effect in cats. Piroxicam is cleared more rapidly in cats than other animals and humans. The intensity of drug binding to plasma protein may also result in differences in highly bound drugs pharmacokinetic [2].

Molecular basis for difference of metabolism in cats
Since last few decades, this difference in metabolism and excretion of drugs in cats in comparison to other species has been studied. The deficiencies in 4 different types of drug elimination pathways are studied like

- Glucuronidation (UGTS)
- Acetylation (NATS)
- Methylation (Thiopurine methyltransferase [TPMT])
- Active transport (ATP-binding cassette G2 [ABCG2])

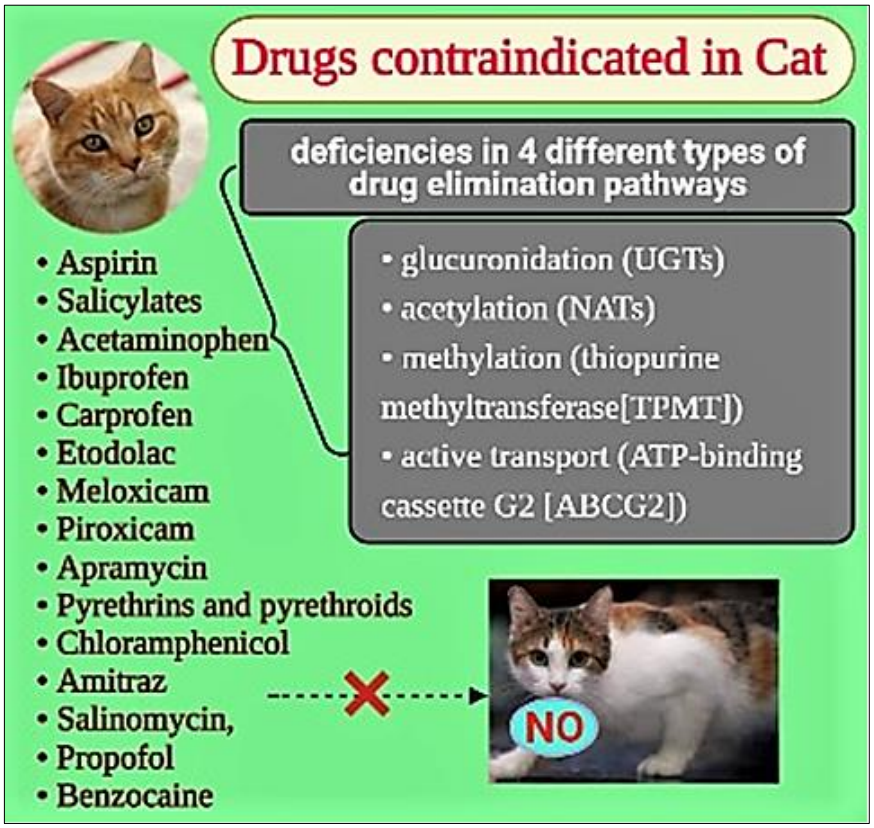

Fig 1: Drugs contraindicated in cats

Table 1: Drugs contraindicated in cats

Types of drugs	Name of the drugs	Description	Mechanism of action	Reason for toxicity	Toxicity symptoms	References
NSAIDs	Aspirin	Salicylate and its salt	Cyclooxygenase enzyme inactivation irreversibly leads to suppression of the thromboxanes & prostaglandins.	Less of glucuronyl transferase and glycine conjugation	Increased bleeding time, fever, vomiting with blood, panting, liver damage, coma, seizures, death.	[1]
	Salicylates	Salt or ester of salicylic acid, food preservatives, antiseptics, acteriostatic, fungicidal keratolytic	Nonselective inhibition of peripherally and centrally mediated cyclooxygenase. Potent inhibitor of thromboxane production function.	Relatively deficient in glucuronosyl transferase, which conjugates salicylate with glucuronic acid.	Lethargy, vomiting, diarrhoea, hematemesis, melena, abdominal pain, asthma, headaches, nasal congestion, itching, skin rash, or hives, Swelling of the hands, feet, and face, Stomach pain Severe gastric ulceration.	[2]
	Acetaminophen (Paracetamol)	Aniline analgesics	Prostaglandin's synthesis is weakly inhibited like selective cyclooxygenase-2 inhibitors and also decreased concentration of prostaglandins.	Deficient in glucuronidation and sulfation abilities, N-acetyl-p-benzoquinoneimine (NAPQI) formed alternatively bind and damage the hepatic cell membrane leading to its injury and death	Depression, weakness, cyanosis, vomiting, tachypnea, facial edema, paw edema, dyspnea, Heinz body anaemia, methemoglobinemia (muddy or brown mucous membrane), hepatotoxicity, nephrotoxicity, death.	[3]

				subsequently.		
	Ibuprofen, carprofen, etodolac	Systemic non-steroidal anti-inflammatory drugs	Inhibition of cyclooxygenase activity, blocking the production of prostaglandins, substances that the body releases in response to illness and injury.	Low capacity for hepatic glucuronidation, needed for elimination.	Gastric and intestinal ulcers, which can bleed tarry stools, and bloody stools, blood dyscrasias renal (kidney) failure and death	[4]
	Meloxicam, Piroxicam	Cyclooxygenase (COX) selective non-steroidal anti-inflammatory drugs oxicam family	Preferential inhibition of COX-2 and sparing COX-1 alone.	Low capacity for hepatic glucuronidation, needed for elimination.	Renal failure and death, serious cardiovascular thrombotic events, including myocardial infarction and stroke.	[5]
Antibiotics	Apramycin	Source: Streptomyces tenebrarius Aminoglycoside antibiotics, bactericidal action. Gram-negative	Inhibition of microbial protein synthesis accomplished through binding to the bacterial 30S small ribosomal subunits	These drugs are concentrated in the labyrinthine fluid and vestibular/cochlear sensory cells and hairs undergo concentration dependent destructive changes.	Ototoxic; cochleotoxicity in auditory system and vestibulotoxicity in vestibular system. Nephrotoxicity, Neuromuscular & renal toxicity	[6]
	Chloramphenicol	Source: Bacterium Streptomyces venezualae in 1947 Broad spectrum antibiotic used for anaerobic infections bacterial infections like conjunctivitis	Inhibition of microbial protein synthesis accomplished through reversibly binding to the 50S subunit of the bacterial ribosome and inhibition of the peptidyl transferase step of protein synthesis.	Needs to be metabolized in liver as Chloramphenicol glucuronide	Reversible marrow suppression, arrest of maturation of myeloid cells and erythroid cells, mitotic activity inhibition	[7, 8]
Antiparasitics	Pyrethrins and pyrethroids	Pyrethrins Source: Chrysanthemum cinerariifolium. Pyrethroids are synthetic analogues of pyrethrins. pyrethroids types – type I: T (tremor) type II: CS (choreoathetosis and salivation). (more toxic)	Axonic excitotoxins, the toxic effects of which are mediated through preventing the closure of the voltage-gated sodium channels in the axonal membranes in muscle and nervous tissue	Lack of the metabolising enzyme glucuronosyl transferase	Muscle fasciculations, hyperaesthesia, seizures, twitches, electrolyte abnormalities, pyrexia, mydriasis, apnoea, temporary blindness, ataxia, hypothermia, cardiorespiratory arrest, aspiration pneumonia,	[9-11]
	Amitraz	Acaricide and tickicide non-systemic acaricide and insecticide and has also been described as a scabicide formamidine pesticide family,	Activates alpha-2 adrenergic receptor in the central nervous system (CNS), alpha2 and alpha1 adrenergic receptor in the peripheral nervous system (PNS).	Stimulation of α2-adrenergic receptors that generates the main signs of amitraz poisoning, such as loss of consciousness, breathing depression, seizures, bradycardia, hypotension, and hypothermia	Bradycardia, CNS depression, hypothermia, mydriasis, vocalization, vomiting, diarrhea, seizures, urination, cardiovascular collapse and respiratory depression	[12-14]
	Salinomycin,	Ionophores: Antibacterial, anti-cancer drugs and coccidiostat	Inhibition of ookinete development, oocyst formation	Polyneuropathy of the peripheral nerves, characterized by	Anorexia, tachycardia ataxia, recumbency, dyspnoea,	[15]

			in the mosquito midgut, blocking their transmission Selectively damages infected erythrocytes.	primary axonal degeneration and secondary degeneration of the myelin sheath resulting in paralysis. hypoxia of the myocardium due to dyspnoea from paralysis of the respiratory musculature	peripheral polyneuropathy, paresis and paralysis	
Anesthetics	Benzocaine	Topical local anesthetics	Stabilizes the neuronal membrane reversibly, decreasing its permeability to sodium ions, inhibition of depolarization of the neuronal membrane blocking of initiation and conduction of nerve impulses.	Due to their unique hemoglobin structure, it is easily damaged	Seizures, tremors and cardiac arrhythmia, Heinz body formation, methemoglobinemia reduced oxygen carrying capacity, hemolytic anemia.	[16]
	Propofol	Intravenous general anaesthetic	Decreases the rate of dissociation of the Gamma-aminobutyric acid (GABA) from the receptor, duration of the GABA-activated opening of the chloride channel increased resulting hyperpolarization of cell membranes.	Lack of glucuronosyl transferase which is needed to glucuronidate propofol.	Metabolic acidosis, bradyarrhythmias, and progressive myocardial failure, Heinz body anemia	[17]

1. UGT deficiency

Glucuronidation is the most important process of metabolism which transfers glucuronic acid to a variety of drugs, toxins, steroids and bilirubuin like endogenous compounds thus promoting better elimination of these compounds into urine and/or bile. The main sites of drug metabolism like liver, kidney, intestinal mucosa express UGT.

The oldest broadly accepted idiosyncrasy of cat is deficient glucuronidation. Literatures as old as 60 years show inability of cat to glucuronidate drugs and toxins [18]. This deficiency in cat is not specific to all glucuronidated drugs but depends on structure of drug. It affects the simple planar phenolic structured drugs which are to be mainly metabolized by UGT1A1, essential for glucuronidation and clearance of bilirubin. UGT1A isoforms like UGT1A6 and UGT1A9 particularly found in liver. 10 different UGT1As are expressed in dogs liver, 9 different UGT1As are expressed in human liver but feline liver have only 2 isoforms (UGT1A1 and UGT1A2) and the UGT1A6 pseudogene. No UGT1A isoform related to UGT1A6 or UGT1A9 was expressed in cat liver.

UGT1A6 gene identification by DNA sequencing proved multiple mutations suggesting a functional UGT1A6 gene present at one point in cats that had been permanently disabled in cat into a pseudogene [19]. Carnivore species (African lion, cheetah, leopard, tiger, leopard, margay, tigrina, lynx, golden cat, bobcat, puma, Florida panther, cat) showed UGT1A6 mutations which evolved them differently them from Carnivora species (wolves, bears, raccoon, ferret) between 11 and 35 million years ago.

Drug like morphine is selectively glucuronidated in humans by UGT2B7 gene. Although Cats express feline orthologs of human UGT2B7 and UGT2B15, it shows reduced morphine glucuronidation which gets compensated by sulfation pathways clearance.

Drug like lorazepam is selectively glucuronidated in humans by UGT2B15 gene but it is glucuronidated speedily in cats as feline ortholog of human UGT2B15 is expressed in cats [20].

Preservative like benzoic acid and Benzyl alcohol (is metabolized to benzoic acid) and excreted as the glucuronide or glycine conjugate in most species. Cats are unable to glucuronidate benzoic acid, but can glycinate it slowly. So, benzyl alcohol used in pharmaceutical preparations for cats are minimized.

2. Glycine deficiency

Drugs like aspirin have slow clearance in cats due to poor glycine conjugation.

3. NAT2 Deficiency

Drugs like isoniazid, many of the sulfonamide antibiotics like sulfamethazine, sulfanilamide, sulfadimethoxine, dapsone, hydralazine, procainamide, acetaminophen need to be acetylated for metabolism. N-Acetylation is catalyzed by the N-acetyltransferase enzymes NAT1 and NAT2. Cats liver lack NAT2, but express NAT1, thus show lower enzyme activity than other species [21]. So, these drugs are acetylated more slowly in cats showing toxicities in cats.

4. TPMT deficiency

Drugs like 6-mercaptopurine for cancer and azathioprine for immunosuppression require S-Methylation by TPMT for metabolism and excretion. Less TPMT activity in cat erythrocytes involving gene sequence differences affect enzyme level and affinity for substrate and activity [22].

5. ABCG2 deficiency

Drugs like Fluoroquinolone antibiotic use ABCG2 transporter for efflux. Due to inefficient efflux by ABCG2 transporter from the feline eye, temporary and subsequently permanent blindness develop in cats [23].

Conclusion

Further molecular level studies are needed to understand the differences in cats in drug metabolism and disposition. It will help in more rational prescribing of prevailing medications, and effective and safer drugs discovery and development for cats. Pet owners of cats should be made aware to avoid these medications either intentionally or accidentally.

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