Drugs contraindicated in cat

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Abstract

While medicating cats, veterinarians have to be very cautious as 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-glucuronyltransferase (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 gliacin 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)
- Methyltransfer (Thiopurine methyltransferase [TPMT])
- Active transport (ATP-binding cassette G2 [ABCG2])

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Fig 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, aceristostatic, 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, diarrhea, hematemesis, melena, abdominal pain, asthma, headaches, nasal congestion, itching, skin rash, or hives, Swelling of the hands, feet, and face. | [2] |
|                | Acetaminophen (Paracetamol) | Aniline analogics | 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-benzoquinoneimin e (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] |
| **Antiparasitics** | **Systemic non-steroidal anti-inflammatory drugs** | **Antibiotics** | **Subsequently.** | **References** |
|-------------------|-----------------------------------------------|-----------------|------------------|---------------|
| Ibuprofen, carprofen, etodolac | Chloramphenicol | Iminosugars | 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. | [4] |
| Meloxicam, Piroxicam | Meloxicam, Piroxicam | Meloxicam, Piroxicam | Preferential inhibition of COX-2 and sparing COX-1 alone. | Low capacity for hepatic glucuronidation, needed for elimination. | [5] |
| Apramycin | Chloramphenicol | Chloramphenicol | Inhibition of microbial protein synthesis accomplished through binding to the bacterial 30S small ribosomal subunits | Needs to be metabolized in liver as Chloramphenicol glucuronide | [6] |
| Pyrethrins and pyrethroids | Pyrethrins and pyrethroids | Pyrethrins and pyrethroids | Inhibition of microbial protein synthesis accomplished through reversibly binding to the bacterial ribosome and inhibition of the peptidyl transferase step of protein synthesis. | Reversible marrow suppression, arrest of maturation of myeloid cells and erythroid cells, mitotic activity inhibition | [7, 8] |
| Antiparasitics | Amitraz | Amitraz | 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 | [9, 11] |
| Salinomycin, Ionophores: Antibacterial, anti-cancer drugs and coccidiostat | Salinomycin, Ionophores: Antibacterial, anti-cancer drugs and coccidiostat | Salinomycin, Ionophores: Antibacterial, anti-cancer drugs and coccidiostat | Inhibition of ookinete development, oocyst formation | Polyneuropathy of the peripheral nerves, characterized by | [12-14] |

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**Antiparasitics**

- **Ibuprofen, carprofen, etodolac**
- **Meloxicam, Piroxicam**
- **Apramycin**
- **Chloramphenicol**
- **Pyrethrins and pyrethroids**
- **Amitraz**
- **Salinomycin, Ionophores: Antibacterial, anti-cancer drugs and coccidiostat**
### 1. UGT deficiency

Glucuronidation is the most important process of metabolism which transfers glucuronic acid to a variety of drugs, toxins, steroids and bilirubin like endogenous compounds thus promoting better elimination of these compounds into urine 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 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, dapsona, hydralazine, procainamide, acetyaminophen need to be acetylated for metabolism. N-Acytlation 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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