

Drug Interactions in Polypharmacy

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You have asked...
What are some of the common drug interactions in polypharmacy?

The expert says...

Numerous human drug interactions can occur during absorption, at the target site, or during hepatic or renal elimination, and may lead to loss of efficacy or increased toxicity.¹ Many of these interactions are likely to occur in dogs and cats as well (see **Drug Interactions in Humans That May Affect Dogs & Cats**, page 26), although relatively few veterinary studies have been conducted. Several key veterinary drugs have high interaction potential.

Cimetidine

Cimetidine, a histamine (H₂)-blocker, is a potent inhibitor of several families of cytochrome P450 enzymes and can also inhibit transporter pumps and decrease the renal excretion of some drugs, including clearance of many drugs, such as theophylline, lidocaine, midazolam, and propranolol.²

Because of many potential cimetidine interactions, alternative H₂-blockers such as famotidine, nizatidine, or ranitidine (not a clinically significant P450 inhibitor at therapeutic concentrations in humans)³ should be chosen instead. Ranitidine and nizatidine have the added advantage of prokinetic effects, which may counteract gastric atony in clinically ill patients.

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H₂ = histamine

Sucralfate

Sucralfate and aluminum-containing antacids form complexes with many drugs in the GI tract, markedly decreasing drug absorption. For example, in humans, absorption of ciprofloxacin, a fluoroquinolone, is reduced by 96% when given with sucralfate; if ciprofloxacin is given 2 hours *after* sucralfate, absorption can still be reduced by less than 50% but is less impaired (about 17%) if ciprofloxacin is given 2 hours *before* sucralfate.^{4,5}

Sucralfate and other aluminum-containing drugs also inhibit the absorption of tetracycline, theophylline, and digoxin.⁶ These physicochemical interactions can also occur in dogs and cats. Because coordinating dosing at home can be difficult, sucralfate should not be used for outpatients being administered oral drugs. The exception is H₂-blockers, for which sucralfate slows but does not decrease the extent of absorption. In humans, sucralfate and H₂-blockers are given simultaneously without loss of efficacy⁶; this may apply to dogs and cats with suspected or documented gastric ulceration.

Ketoconazole

Ketoconazole, an antifungal, inhibits a specific cytochrome P450 enzyme family (*CYP3A*) that has a wide substrate range and high potential for drug–drug interactions in humans, dogs, and cats. Ketoconazole inhibits P-glycoprotein, the important drug efflux transporter in the GI tract, kidney(s), biliary tree, and brain. Therefore, ketoconazole can decrease the bioavailability and/or clearance of many drugs.

For example, ketoconazole increases blood cyclosporine concentrations, which can allow lower therapeutic doses of cyclosporine (less expensive for clients). The recommended starting doses are cyclosporine at 2.5 to 5 mg/kg q12–24h (depending on disease severity) and ketoconazole at 5 to 10 mg/kg q24h.⁷ Trough cyclosporine concentrations can be measured at a steady state after 5 days of treatment.⁷

Ketoconazole also doubles ivermectin exposure (based on area under the curve) in dogs.⁸ Neurologic toxicity has not been reported but could occur if ketoconazole was combined with high doses of ivermectin (eg, in treating sarcoptic mange) or given to P-glycoprotein–deficient (*ABCB1* deletion) breeds.

Other drugs that affect serotonin include tramadol and dextromethorphan (both of which inhibit serotonin reuptake).

Other drugs that show impaired clearance with ketoconazole include clomipramine, amitriptyline, midazolam, alprazolam, zonisamide, cisapride, fluoxetine, and vinblastine.⁹ Like ketoconazole, itraconazole inhibits the cytochrome P450 metabolism of cyclosporine, midazolam, alprazolam, and zonisamide in humans.⁹

Fluoroquinolones

Fluoroquinolone antibiotics inhibit the clearance of theophylline. This has led to theophylline toxicosis in humans and is attributed to inhibition of the cytochrome P450 enzyme *CYP1A2*. In dogs, enrofloxacin can lead to 30% to 50% higher plasma theophylline concentrations,¹⁰ and marbofloxacin at 5 mg/kg can increase theophylline exposure by about 28%.¹¹

Oral absorption of fluoroquinolones is impaired by drugs that contain divalent or trivalent cations, such as aluminum (eg, sucralfate, aluminum hydroxide, aluminum carbonate), calcium carbonate, oral zinc, oral iron, and magnesium (eg, vitamin supplements). This can lead to decreased fluoroquinolone concentrations and potential therapeutic failure.

H₂ = histamine, MAOI = monoamine oxidase inhibitor



Omeprazole

Omeprazole, a proton-pump inhibitor, inhibits some cytochrome P450 enzymes in humans (primarily *CYP2C19*) and may inhibit the clearance of some drugs, including diazepam, midazolam, warfarin, and carbamazepine. Omeprazole also impairs conversion of clopidogrel, an antiplatelet agent, to its active metabolite in humans, leading to decreased antiplatelet efficacy and increased risk for ischemic cardiac events.¹² Omeprazole may also lead to digoxin toxicosis, possibly via inhibition of P-glycoprotein efflux of digoxin.¹³

As a potent inhibitor of gastric acid secretion, all proton pump blockers can decrease the absorption of compounds that require an acidic pH for optimal absorption, including iron supplements, oral zinc, ketoconazole, and itraconazole. This same interaction also applies to H₂-blockers (eg, famotidine). Discontinuing antacids when ketoconazole or itraconazole is being given may be wise. Alternatively, if antacids cannot be discontinued, fluconazole can be considered if indicated, as fluconazole absorption is not affected by changes in gastric pH.^{14,15}

Phenobarbital

Phenobarbital, an anticonvulsant, is a major P450 enzyme inducer in humans and dogs. Phenobarbital accelerates the metabolism of many drugs, including ketoconazole, clomipramine, and lidocaine. Phenobarbital also accelerates the clearance of mitotane; therefore, dogs on both phenobarbital

Useful Resources to Help Screen for Potential Drug Interactions

- **Drug Interactions Checker** (drugs.com/drug_interactions.html)
User-friendly but contains only human data
- **PubMed** (ncbi.nlm.nih.gov/pubmed)
Can be used to search for both veterinary and human drug studies

and mitotane often need much higher loading and maintenance doses of mitotane for hyperadrenocorticism treatment. In cats, however, phenobarbital causes minimal cytochrome P450 enzyme induction,^{16,17} and P450-mediated drug interactions with phenobarbital are unlikely.

Clomipramine

Clomipramine, a tricyclic antidepressant, inhibits both norepinephrine and serotonin reuptake. Clomipramine can lead to serotonin accumulation and serotonin syndrome (clinically seen as twitching, tremor, tachycardia, myoclonic movements, and hyperthermia) in humans when used in combination with monoamine oxidase inhibitors (MAOIs, which decrease the breakdown of serotonin) or serotonin reuptake inhibitors, which increase synaptic serotonin concentrations. Deaths have been reported in humans given clomipramine plus MAOIs—a well-established interaction. Veterinary MAOIs include L-deprenyl (selegiline) and amitraz.

Other drugs that affect serotonin include tramadol and dextromethorphan (both of which inhibit serotonin reuptake). However, the interaction potential with these weaker serotonergic drugs appears much lower in humans.

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Ketoconazole increases blood cyclosporine concentrations, which can allow lower doses of cyclosporine at less cost to owners.

Closing Remarks

Based on what is known for human patients, these drugs pose reasonable risk for adverse drug interactions in dogs and cats. The accompanying drug history should be reviewed carefully when these drugs are administered. Veterinarians should obtain

a complete and updated drug history at each office visit, but this is especially important when new drugs are being prescribed or a patient is not well. ■ **cb**

See **Aids & Resources**, back page, for references & suggested reading.

TX at a Glance

Drug Interactions in Humans That May Affect Dogs & Cats

Drug	May Increase Toxicity of	May Decrease Efficacy of	Efficacy May Be Decreased by
Cimetidine	Alprazolam, diazepam, lidocaine, midazolam, procainamide, propranolol, theophylline, warfarin	Iron supplements, itraconazole, ketoconazole	
Clomipramine	Amitraz, fluoxetine, selegiline		
Fluoroquinolones	Theophylline		Aluminum, calcium, iron, magnesium, sucralfate
Ketoconazole	Amitriptyline, cisapride, cyclosporine, digoxin, midazolam, warfarin		Antacids, H ₂ -blockers, omeprazole
Omeprazole	Carbamazepine, diazepam, digoxin, midazolam, warfarin	Clopidogrel, itraconazole, ketoconazole, oral iron, oral zinc	
Phenobarbital		Clomipramine, digoxin, lidocaine, mitotane, propranolol, theophylline	
Sucralfate		Azithromycin, digoxin, fluoroquinolones, tetracyclines, theophylline	