Top Ten Potential Drug Interactions in Dogs and Cats

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In humans, the risk of adverse drug interactions multiplies as the number of administered drugs increases. Interactions can occur during IV drug administration, during oral absorption, at the target site, or during hepatic or renal elimination, and may lead to loss of efficacy or increased toxicity. Although most of our knowledge of drug interactions is from data in humans, many of these interactions are likely to occur in dogs and cats as well.

Cimetidine

Cimetidine is a major P450 enzyme inhibitor, and also decreases renal excretion of some drugs by inhibiting transporter pumps. Cimetidine therefore decreases the clearance of many drugs:

- Theophylline and aminophylline: theophylline toxicity seen in humans
- Lidocaine: could lead to GI and neurologic side effects
- Midazolam: increased plasma midazolam concentrations with cimetidine
- Warfarin: do not use cimetidine in suspected warfarin toxicity patients
- Propranolol (but not atenolol)

Because of many potential cimetidine interactions, alternative H_2 blockers such as ranitidine, famotidine, or nizatidine (which are not P450 inhibitors at therapeutic concentrations), should be chosen over cimetidine. Ranitidine and nizatidine have the added advantage of prokinetic effects, which may counteract gastric atony in clinically ill patients.

Sucralfate

Aluminum-containing drugs such as sucralfate can form complexes with many other drugs in the GI tract, markedly decreasing drug absorption:

- Fluoroquinolones: poor bioavailability even 6 hours after sucralfate in humans
- Tetracycline and doxycycline: marked inhibition of oral absorption
- Theophylline, aminophylline, digoxin, azithromycin: sucralfate may decrease efficacy
- H_2 blockers: sucralfate delays, but does not decrease the extent of, the absorption of H_2 blockers; therefore staggering of dosing is probably <u>not</u> required

This is a physicochemical interaction that is likely to occur in dogs and cats as it does in humans. It is recommended that sucralfate be avoided in patients on multiple oral drugs, particularly tetracyclines and fluoroquinolones. If sucralfate must be given orally with drugs other than H2 or pump blockers, the sucralfate should be given 2 hours after the other drugs (not vice versa), and at least 6-8 hours before subsequent dosing of other drugs that day. Because of the difficulty in coordinating dosing at home, I avoid sucralfate on an out-patient basis unless the only other drugs given are H2 or pump blockers.

Ketoconazole

Ketoconazole and itraconazole are best absorbed at acidic pH; therefore, do not combine these drugs with antacids such as:

- Omeprazole, H_2 blockers, or aluminum hydroxide
    - However, antacids do not affect the absorption of fluconazole (Zimmermann 1994)

Ketoconazole inhibits a specific cytochrome P450 enzyme, CYP3A, that has a wide substrate range and high potential for drug-drug interactions. This has been shown in both dogs and cats. Ketoconazole is also an inhibitor of p-glycoprotein, the important drug efflux transporter in the gut, kidney, biliary tree, and brain. Ketoconazole can therefore decrease the bioavailability and/or clearance of many drugs:

- Cyclosporine: a favorable interaction; ketoconazole can allow lower doses of cyclosporine. Recommended dosages: cyclosporine, 5 mg/kg/day; ketoconazole, 10 mg/kg/day. Monitor ALT and clinical response. Whole blood cyclosporine can be measured at steady state (by one week). Target levels for immunosuppression in humans are 400-600 ng/ml, but dogs with perianal fistulas may respond to much lower concentrations.
- Ivermectin: ketoconazole doubles ivermectin exposure (AUC) in dogs (Hugnet 2007); neurologic toxicity has not been reported, but could occur if ketoconazole were combined with high dosages of ivermectin (e.g. in treating sacroptic mange), or in p-glycoprotein deficient breeds.
- Clomipramine, amitriptyline, midazolam, fluoxetine: decreased clearance; ketoconazole could increase sedation
- Warfarin: ketoconazole may prolong its toxicity

Note: Itraconazole, like ketoconazole, also inhibits the P450 metabolism of these same drugs in humans. Fluconazole has less P450 inhibition, but can still affect drug clearance at dosages > 3 mg/kg/day in humans.

Fluoroquinolones

Oral absorption of fluoroquinolones is impaired by drugs that contain divalent or trivalent cations, such as:

- Sucralfate, aluminum hydroxide, aluminum carbonate
- Calcium carbonate
- Oral zinc (in the milk thistle supplement Marin®; 17-45 mg zinc per tablet)
- Oral iron or magnesium (e.g. in vitamin supplements)

In humans and dogs, fluoroquinolones inhibit the metabolism, by CYP1A2, of theophylline. This has led to theophylline toxicity in humans.

- In dogs, enrofloxacin leads to higher plasma theophylline concentrations by about 30-50% (Intorre 1995), while marbofloxacin at 5 mg/kg decreases theophylline clearance to a lesser extent (about 26%; Hirt 2003)
- Fluoroquinolones also inhibit the clearance of pentoxifylline (shown in mice).

Metoclopramide

As a dopaminergic (D2) antagonist and prokinetic agent, metoclopramide has several important drug interactions:

- Enhanced absorption of acetaminophen, aspirin, and alcohol overdoses via increased gastric emptying (shown in humans).
- Increased plasma concentrations of cyclosporine (by 30%) in humans (possibly due to enhanced gastric emptying). However, this was not seen in dogs after a single dose of metoclopramide (Radwanski 2011)
- Extrapyramidal side effects (tremor) in combination with phenothiazines (e.g. chlorpromazine, acepromazine) or selective serotonin reuptake inhibitors (e.g. fluoxetine)
- Tremor in patients with renal insufficiency, unless dosage is reduced.
- Metoclopramide reduces the amount of propofol needed for anesthetic induction in humans by 20-25% (Page 1997; mechanism unknown).

As a D2 antagonist, metoclopramide should not affect D1-mediated vascular effects of administered dopamine:

- No effect on dopamine systemic pressor effects in dogs (Hahn 1980)
- However, metoclopramide (1 mg/kg) did attenuate dopamine-mediated renal vasodilation in dogs, but only for 30 minutes (Hahn 1980)

Cisapride

Like ketoconazole, cisapride is a substrate of CYP3A. High plasma concentrations of cisapride have led to fatal cardiac arrhythmias in humans (prolonged QT syndrome).

- Prolongation of the QT interval has been shown at very high cisapride dosages (30 mg/kg BID) in cats. This would be a concern primarily for accidental drug overdose.
- Azole antifungal drugs (fluconazole, itraconazole, ketoconazole) that inhibit CYP3A could increase cisapride concentrations and increase the risk of cardiac side effects, as shown in humans
- Erythromycin increases cisapride concentrations (humans only)
    - Erythromycin does not affect cisapride in dogs (Al-Wabel 2002), and is not an inhibitor of CYP3A in cats (Shah 2009).
- Mosapride, a newer prokinetic drug, does not affect the QT interval on ECG measurements in cats (Kii 2001).
    - The pharmacologically effective dosage of mosapride in dogs is 0.75 – 2.0 mg/kg BID (Tsukamoto 2011); this has not been evaluated in cats.

Furosemide

Several drug combinations with furosemide can lead to enhanced toxicity:

- Aminoglycoside nephrotoxicity is enhanced by furosemide. (Adelman 1979)
    - Mannitol may be preferable to furosemide for treatment of acute renal failure due to aminoglycosides such as amikacin and gentamicin.
- Enalapril and benazapril may cause hemodynamic changes leading to acute renal failure from high doses of furosemide.
    - Delay the start of ACE inhibitors until fulminant heart failure is resolved and furosemide dosages are lowered to maintenance dosing
- Digoxin: furosemide increases risk of digoxin toxicity
    - Furosemide can lead to pre-renal azotemia anddecreased digoxin excretion.
    - Furosemide can also lead to hypokalemia and hypomagnesemia, both of which exacerbate the cardiac toxicity of digoxin.
    - Serum digoxin levels need to be monitored in all dogs on digoxin.
- Renal function and serum electrolytes should be routinely evaluated in all patients on furosemide.

Other drug combinations with furosemide can affect efficacy:

- Lidocaine
    - Hypokalemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine. Serum potassium should be evaluated in patients with ventricular arrhythmias, and potassium supplementation should be considered if patients do not respond to lidocaine.
- Bromide
    - Furosemide administration will increase the renal loss of bromide, and lower serum bromide concentrations, which can lead to seizure breakthrough.

Omeprazole

Omeprazole is an inhibitor of some P450's in humans (mostly CYP2C19), and may inhibit the clearance, and possibly increase the toxicity, of:

- Diazepam, midazolam, warfarin, and carbamazepine.
- Omeprazole also impairs conversion of clopidogrel to its active metabolite, leading to decreased anti-platelet efficacy in humans
    - Proton pump inhibitors have led to adverse cardiovascular events (loss of clopidogrel efficacy) in human patients (Bhurke 2012)
- Omeprazole may also lead to digoxin toxicity, possibly via inhibition of p-glycoprotein efflux of digoxin (Kiley 2007).

As an inhibitor of gastric acid secretion, all proton pump blockers can decrease the absorption of:

- Iron supplements, oral zinc
- Ketoconazole and itraconazole
    - But not fluconazole, which does not require an acidic pH for absorption
- It is wise to discontinue antacids when ketoconazole and itraconazole are being given. Alternatively, if antacids cannot be stopped, fluconazole can be considered, if indicated.

Phenobarbital

Phenobarbital is a major P450 enzyme *inducer* in humans and dogs. Phenobarbital speeds the metabolism of many drugs in dogs, including:

- Glucocorticoids – but does not affect LDDST testing
- Ketoconazole, chloramphenicol
- Clomipramine
- Theophylline
- Digoxin, propranolol, lidocaine
- Mitotane
    - Dogs on phenobarbital, that are given mitotane for hyperadrenocorticism, often need much higher loading and maintenance dosages of mitotane.

However, phenobarbital causes minimal cytochrome P450 enzyme induction in the cat (Maugras 1979; Truhaut, 1978), and therefore P450-mediated drug interactions with phenobarbital are unlikely in the cat.

Clomipramine

As a tricyclic antidepressant, clomipramine inhibits both norepinephrine and serotonin reuptake. Clomipramine can lead to serotonin accumulation and "serotonin syndrome" (twitching, tremor, tachycardia, myoclonic movements, hyperthermia) in humans, when used in combination with drugs such as:

- Monoamine oxidase inhibitors (MAOIs, which decrease the breakdown of serotonin)
    - Deaths reported in humans given clomipramine plus MAOIs; well established interaction
        - Veterinary MAOIs include:
        - L-deprenyl (selegiline)
        - Amitraz: found in tick dips and some collars
- AVOID these in dogs taking clomipramine
- Serotonin reuptake inhibitors (which increase synaptic serotonin concentrations)
    - Fluoxetine (Prozac, Reconcile)
    - Fluoxetine has been associated with serotonin syndrome in combination with clomipramine in human case reports
- Other drugs that affect serotonin:
    - Tramadol: inhibits serotonin reuptake; *potential* interaction with clomipramine
    - Dextromethorphan (in Robitussin): inhibits serotonin reuptake; *potential* interaction with clomipramine

Drug interactions in humans that may also affect dogs and cats

Drug	May increase the toxicity of:	May decrease the efficacy of:	Toxicity may be increased by:	Efficacy may be decreased by:
Cimetidine	Theophylline, lidocaine, midazolam, propranolol	Ketoconazole, itraconazole, iron supplements		
Sucralfate		Fluoroquinolones, tetracyclines, theophylline, digoxin		
Ketoconazole	Cyclosporine, warfarin, digoxin, amitriptyline, midazolam, cisapride			Antacids, H_2 blockers, omeprazole
Fluoro-quinolones	Theophylline			Sucralfate, iron, calcium, aluminum, magnesium
Metoclopramide	Ethanol, aspirin, or acetaminophen overdoses; propofol?		Aceprozamine, fluoxetine (tremor)	
Furosemide	ACE inhibitors, digoxin, aminoglycosides	Bromide, lidocaine (via hypokalemia)	Aminoglycosides	Some NSAIDs
Cisapride			Azole antifungals, fluoxetine	
Omeprazole	Diazepam, warfarin, digoxin	Ketoconazole, itraconazole, iron supplements		
Phenobarbital		Mitotane, clomipramine, lidocaine, propranolol, theophylline, digoxin…		
Clomipramine	Selegiline, amitraz, fluoxetine		Fluoxetine, ketoconazole, itraconazole; possibly tramadol, dextromethorphan	