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Next WSAVA Congress:

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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 decreases the clearance of many drugs:

- Chloramphenicol: risk of dose-dependent leukopenia
- Metronidazole: risk of neurologic side effects
- Lidocaine: enhanced GI and neurologic side effects
- Theophylline and aminophylline: theophylline toxicity
- Warfarin, propranolol, diazepam, midazolam, many others

Until more is known about cimetidine interactions, alternative H2 blockers such as ranitidine, famotidine, or nizatidine (which are not P450 inhibitors at therapeutic concentrations), should be chosen over cimetidine for patients treated with multiple drugs. 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
- H2 blockers: sucralfate delays, but does not decrease the extent of, the absorption of H2 blockers; therefore staggering of dosing is probably NOT required
- Theophylline, aminophylline, digoxin, azithromycin: sucralfate may decrease efficacy.

This is a physicochemical interaction that is likely to occur in dogs and cats as it does in humans.

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

- Omeprazole, H2 blockers, or antacids
- Interestingly, increased gastric pH does not affect the absorption of fluconazole

Ketoconazole inhibits a cytochrome P450 enzyme (CYP3A), with a wide substrate range and high potential for drug-drug interactions. Ketoconazole is also an inhibitor of p-glycoprotein, an important drug efflux transporter in the gut and biliary tree. 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.
- Digoxin: ketoconazole can lead to digoxin toxicity
- Amitriptyline, midazolam: ketoconazole could increase sedation
- Warfarin: ketoconazole may prolong its toxicity

Note: Itraconazole, like ketoconazole, also inhibits the P450 metabolism of the same drugs in humans.

Fluoroquinolones
The absorption of oral fluoroquinolones is markedly impaired by drugs that contain divalent or trivalent cations, such as:

- Sucralfate, aluminum hydroxide, aluminum carbonate
- Calcium carbonate
- Oral iron, zinc

In humans and dogs, fluoroquinolones inhibit the CYP1A2 metabolism of theophylline. This has lead to theophylline toxicity in humans. In dogs, enrofloxacin leads to higher theophylline concentrations by about 30-50%.

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).
- Enhanced extrapyramidal side effects (tremor) in combination with phenothiazines (e.g., chlorpromazine, acepromazine) or selective serotonin reuptake inhibitors (e.g., fluoxetine), or with renal insufficiency.
- Metoclopramide reduces the amount of propofol
needed for anesthetic induction in humans by 20-25% (mechanism unknown).

It has been suggested that metoclopramide may antagonize the effects of dopamine on renal hemodynamics. However:
- Metoclopramide has no effect on low dose dopamine-induced increases in GFR or effective renal plasma flow in humans.
- Dopamine increases urine output in cats as in humans, and this is not inhibited by dopamine antagonists.

Cisapride

Like ketoconazole, cisapride is a substrate of CYP3A. High plasma concentrations of cisapride can lead to potentially fatal cardiac arrhythmias in humans. Drugs that inhibit CYP3A may increase cisapride concentrations and increase the risk of cardiac side effects in humans:
- Clarithromycin, erythromycin (but not azithromycin)
- Fluconazole, itraconazole, ketoconazole

Note: in one study in dogs, erythromycin did not alter cisapride pharmacodynamics.

Furosemide

Several drug combinations with furosemide can lead to enhanced toxicity:
- Amikacin and gentamicin: nephrotoxicity is enhanced by furosemide; mannitol may be preferable to furosemide for treatment of acute renal failure due to aminoglycosides
- Enalapril, benazapril: may cause hemodynamic changes leading to acute renal failure, when given with full doses of furosemide. Use conservative initial doses of ACE inhibitors when also starting furosemide.
- Digoxin: furosemide increases serum digoxin levels (independent of dehydration). Furosemide can also lead to hypokalemia and hypomagnesemia, both of which exacerbate the cardiac toxicity of digoxin. In addition, furosemide can lead to pre-renal azotemia, leading to decreased digoxin excretion. All of these interactions can lead to digoxin toxicity unless serum digoxin levels are monitored.
- Renal function and serum electrolytes should be routinely evaluated in all patients on furosemide.

<table>
<thead>
<tr>
<th>Drug</th>
<th>May increase the toxicity of:</th>
<th>May decrease the efficacy of:</th>
<th>Toxicity may be increased by:</th>
<th>Efficacy may be decreased by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Metronidazole, lidocaine, theophylline, diazepam, propranolol</td>
<td>Ketoconazole, itraconazole, iron supplements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucralfate</td>
<td></td>
<td>Fluoroquinolones, tetracyclines, erythromycin, theophylline, digoxin</td>
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</tr>
<tr>
<td>Ketoconazole</td>
<td>Cyclosporine, warfarin, digoxin, amitriptyline, midazolam, cisapride</td>
<td></td>
<td>Antacids, H₂ blockers, omeprazole</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Theophylline</td>
<td></td>
<td>Sucralfate, iron, calcium, aluminum, magnesium</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Ethanol, aspirin, or acetaminophen overdoses, propofol?</td>
<td>Probably does not counteract the renal effects of dopamine</td>
<td>Aceprozamine, fluoxetine (tremor)</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>ACE inhibitors, digoxin, aminoglycosides</td>
<td>Bromide, lidocaine (via hypokalemia)</td>
<td>Aminoglycosides</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Cisapride</td>
<td></td>
<td></td>
<td>Clarithromycin, erythromycin,azole antifungals, fluoxetine</td>
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<tr>
<td>Omeprazole</td>
<td>Diazepam, warfarin, digoxin</td>
<td>Ketoconazole, itraconazole, iron supplements</td>
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<tr>
<td>Phenobarbital</td>
<td></td>
<td>Glucocorticoids, clomipramine, lidocaine, theophylline, digoxin, propranolol...</td>
<td></td>
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</tr>
</tbody>
</table>

Table. Drug interactions in humans that may also affect dogs and cats.
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 instituted if patients do not respond to lidocaine.
- Bromide: furosemide administration will increase the renal loss of bromide, and lower serum bromide concentrations, which may lead to seizure breakthrough.

**Omeprazole**

Omeprazole is an inhibitor of some P450s in humans, and may inhibit the metabolism, and possibly increase the toxicity of:
- Diazepam, midazolam
- Warfarin
As an inhibitor of gastric acid secretion, omeprazole can also decrease the absorption of:
- Iron supplements
- Ketoconazole and itraconazole (but not fluconazole, which does not require an acidic pH for absorption)

**Phenobarbital**

Phenobarbital is a major P450 enzyme inducer in humans and dogs. Phenobarbital speeds the metabolism of many drugs in dogs, including:
- Glucocorticoids, ketoconazole, clomipramine, chloramphenicol, lidocaine, etodolac, theophylline, digoxin, propranolol, and many others...

However, phenobarbital causes minimal cytochrome P450 enzyme induction in the cat, and therefore these P450-mediated drug interactions are unlikely in the cat.

**Clomipramine**

As a tricyclic antidepressant that inhibits norepinephrine reuptake, clomipramine can have pharmacologic interactions with monoamine oxidase inhibitors (which decrease the breakdown of norepinephrine and serotonin):
- L-deprenyl (selegiline): MAO inhibitors like L-deprenyl used in combination with clomipramine or amitriptyline can lead to ‘serotonin syndrome’ (twitching, tremor, seizures) in humans
- Amitraz: an MAO inhibitor found in tick dips and collars; potential for interaction with tricyclic antidepressants like clomipramine

The metabolism of clomipramine can be inhibited by:
- Fluoxetine (Prozac): can lead to increased clomipramine levels and cardiac conduction disturbances in humans
- Ketoconazole, itraconazole

**References**

Available on request