Fecava lecture*

Top Ten Potential Drug Interactions in Small Animal Medicine

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SUMMARY

Today, comorbidities are increasingly diagnosed in veterinary patients and multiple drug combinations are common. However, as the number of administered drugs increases, so too does the risk for adverse drug interactions. Much of what is known about drug-drug interactions is taken from the human literature, but a growing body of work in veterinary medicine also exists. The purpose of this review is to summarize the current knowledge of potential drug interactions in humans and dogs for ten 'at risk' drugs used in small animal medicine: cimetidine, sucralfate, ketoconazole, fluoroquinolone antibiotics, omeprazole, phenobarbital, clomipramine, furosemide, metoclopramide, and cyclosporine. Increased awareness of these potential drug interactions will enhance therapeutic decision-making and improve the level of care for veterinary patients.

Key words: drug-drug interaction, drug metabolism, adverse drug reaction, polypharmacy

*This paper is based on the FECAVA lecture delivered at the 22nd EuroCongress in Vienna, Austria in June 2016. *Eur J Comp An Pract (Winter 2016) 26(4)*; p9-p19. Go to http://www.ejcap.org for the interactive online presentation of this paper

Introduction

In humans, the risk of adverse drug interactions multiplies as the number of administered drugs increases. Drug interactions may lead to loss of efficacy or increased toxicity. Interactions can occur during intravenous drug administration, during oral absorption, at the target site, or during hepatic or renal elimination [1]. Although most of our knowledge of drug interactions comes from data in humans, many of these interactions are likely to occur in dogs and cats as well. An overview of the top ten potential drug interactions in dogs and cats is provided in table 1.

Cimetidine

Cimetidine, a histamine (H2) blocker often used to prevent and treat gastrointestinal ulcers, is a potent inhibitor of several families of cytochrome P450 enzymes in humans, including CYP2D6 and CYP3A4 [2]. Cimetidine can also inhibit transporter pumps and decrease the renal tubular secretion of some drugs [3]. Cimetidine decreases the clearance of many drugs to variable degrees in humans, including theophylline [4,5], lidocaine [6], midazolam [7,8], propranolol [6,9], metronidazole [10] and others. Cimetidine appears to be a much weaker inhibitor of P450s in dogs [11], but effects on renal transporters have not been well studied. Only a few drugs have been studied in dogs, with no effects on the clearance of clorazepate [12] or methadone [13], modestly delayed clearance of theophylline [14], and delayed absorption of cyclosporine [15].

Because of potential drug interactions with cimetidine, alternative H2 blockers such as ranitidine, famotidine or nizatidine (which are not P450 inhibitors at therapeutic

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Table 1: Potential drug interactions in small animal patients

	Drugs	May increase the toxicity of:	May decrease the efficacy of:	Toxicity may be increased by:	Efficacy may be decreased by:
1	**Cimetidine**	Metronidazole, lidocaine, theophylline, diazepam, propranolol	Ketoconazole, itraconazole, iron supplements		
2	**Sucralfate**		Fluoroquinolones, tetracyclines, erythromycin, theophylline, digoxin		
3	**Ketoconazole**	Cyclosporine, warfarin, digoxin, amitriptyline, midazolam, cisapride, clomipramine, colchicine			Antacids, H2 blockers, omeprazole
4	**Fluoroquinolones**	Theophylline, flunixin meglumine	Mycophenolate mofetil		Sucralfate, iron, calcium, aluminium, magnesium
5	**Omeprazole**	Diazepam, midazolam, carbamazepine, warfarin, digoxin	Ketoconazole, itraconazole, iron supplements, clopidogrel		
6	**Phenobarbital**		Glucocorticoids, clonazepam, clomipramine, lidocaine, etodolac, theophylline, digoxin, propranolol, mitotane, zonisamide, levetiracetam	Chloramphenicol	
7	**Clomipramine**	Selegiline, amitraz		Fluoxetine, ketoconazole, itraconazole, tramadol, dextromethorphan	
8	**Furosemide**	ACE inhibitors, digoxin, aminoglycosides	Bromide, lidocaine (via hypokalemia)	Aminoglycosides	NSAIDs
9	**Metoclopramide**	Ethanol, aspirin, or acetaminophen overdoses; propofol?	Probably does not counteract the renal effects of dopamine	Aceprozamine, fluoxetine	
10	**Cyclosporine**			Ketoconazole, itraconazole, fluconazole, diltiazem, clarithromycin, powdered grapefruit	St. John's wort

concentrations) may have a theoretical advantage [16]. Ranitidine and nizatidine have the added advantage of modest prokinetic effects, which may counteract gastric atony in clinically ill patients [17-19].

Sucralfate

Sucralfate, another antiulcer medication, binds many drugs in the GI tract through its aluminium moiety, forming insoluble complexes and markedly decreasing absorption [20]. For example, the relative bioavailability of doxycycline, a tetracycline antibiotic, is reduced to 20% when given with sucralfate suspension in dogs [21]. Similar results have been documented for minocycline [22]. Sucralfate decreases ciprofloxacin absorption in humans and dogs, although wide inter-individual variation in ciprofloxacin bioavailability likely modulates this effect in dogs [23-26]. Interestingly, sucralfate does not appear to alter absorption of enrofloxacin in dogs [26].

Sucralfate inhibits the absorption of theophylline, digoxin and azithromycin in humans [20,27-28], and these physicochemical interactions likely occur in dogs and cats as well. Impaired absorption of some drugs has also been reported with co-administration of other compounds containing divalent or trivalent cations, including aluminum and magnesium hydroxide [29] and ferrous sulfate [30-31].

Sucralfate drug interactions can be lessened by giving the second drug two hours before the sucralfate, but the opposite regimen is not recommended (i.e. giving the sucralfate first, followed two hours later by the other drug) because of the persistence of sucralfate in the stomach [21-24]. However, because of the difficulty in coordinating dosing at home, sucralfate should be prescribed only with careful thought when other oral drugs are being given. The exception to this is H2 blockers, for which sucralfate slows but does not decrease the extent of absorption. In humans, sucralfate and H2 blockers are given together without loss of efficacy [32-33].

Ketoconazole

The antifungals ketoconazole and itraconazole are best absorbed at acidic pH; therefore, these drugs should not be combined with omeprazole, H2 blockers or other antacids [34]. It is probably wise to discontinue antacids when ketoconazole or itraconazole is being given. Alternatively, if antacids cannot be discontinued, fluconazole can be considered, if indicated, since fluconazole absorption is not affected by changes in gastric pH [35-36].

Ketoconazole also inhibits the cytochrome P450 enzyme family, CYP3A, which has a wide substrate range and high potential for drug-drug interactions [11,37-38]. Further, ketoconazole is an inhibitor of p-glycoprotein, an important drug efflux transporter in the intestine, kidney, and biliary tree, and a component of the blood-brain barrier [39]. Ketoconazole can therefore decrease the bioavailability and/or clearance of many drugs. For example, ketoconazole co-administration doubles ivermectin exposure (based on area under the curve) in dogs [40]. Although not currently reported, neurologic toxicity could occur if ketoconazole were combined with high doses of ivermectin (e.g. in treating sarcoptic mange) or in p-glycoprotein–deficient breeds [41-42]. Other drugs with impaired clearance from ketoconazole in humans include digoxin [43], amitriptyline [44], midazolam [45-46], clomipramine [47] and cyclosporine [48-49] (See Cyclosporine). A case of suspected ketoconazole-potentiated colchicine toxicity was also recently reported in a Chinese shar pei dog [50].

Fluoroquinolones

Fluoroquinolone antibiotics inhibit the clearance of theophylline [51-52] This has led to theophylline toxicosis in humans, and is attributed to inhibition of the cytochrome P450 enzyme CYP1A2 [51]. Fluoroquinolones also inhibit CYP1A activity in dogs in vitro. Consistent with this, in vivo studies in dogs have demonstrated that plasma theophylline concentrations are increased 30–50% by enrofloxacin [52], 28% by marbofloxacin [53], and 37% by ofloxacin [54].

Other fluoroquinolone drug interactions occur independently of cytochrome P450s. Enrofloxacin delays elimination of flunixin meglumine, possibly by competitive inhibition of renal tubular transporters, leading to higher flunixin blood concentrations in dogs [55]. In humans, ciprofloxacin decreases blood concentrations of mycophenolate mofetil, an immunosuppressive agent, by impaired enterohepatic recirculation of mycophenolic acid (MPA) [56]. MPA is excreted in bile as a glucuronidated metabolite, which is deconjugated by brush border enzymes and subsequently reabsorbed. Ciprofloxacin inhibits this glucuronidase activity, preventing MPA reabsorption [56]. Finally, di- and trivalent cation-containing medications can decrease absorption of some fluoroquinolones, causing decreased plasma concentrations and possible loss of efficacy (see Sucralfate).

Omeprazole

The antacid drug omeprazole, a proton-pump inhibitor, inhibits some cytochrome P450 enzymes in humans (primarily CYP2C19) and may inhibit the clearance of some drugs, including diazepam [57-59], midazolam [60], warfarin [61,62] and carbamazepine [63]. Omeprazole may also lead to digoxin toxicosis, possibly via inhibition of P-glycoprotein efflux of digoxin [64-65]. These interactions have yet to be evaluated in dogs or cats.

Omeprazole impairs conversion of the antiplatelet drug clopidogrel to its active metabolite in humans, leading to decreased antiplatelet efficacy and an increased risk for ischemic cardiac events in human patients [66-68]. However, a recent study in dogs showed that omeprazole at a dosage of 1 mg/kg q 24h did not significantly reduce the antiplatelet effects of clopidogrel [69].

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 [70], oral zinc [71], ketoconazole [35] and itraconazole [36]. This same interaction would also apply to H2 blockers such as famotidine, although proton pump inhibitors have a greater antacid effect than H2 blockers in dogs and cats [72-74].

Phenobarbital

The barbiturate phenobarbital is a major P450 enzyme inducer in humans and dogs. Phenobarbital speeds the metabolism of many drugs in humans, including glucocorticoids [75], clonazepam [76], lidocaine [77], etodolac [78], theophylline [79-81] and digoxin [82-83]. Phenobarbital also induces mitotane clearance, and can lead to higher mitotane dosage requirements in dogs being treated for hyperadrenocorticism [84]. Conversely, chloramphenicol is a major inhibitor of phenobarbital clearance and can lead to sedation in dogs being treated with phenobarbital [85-86]. In cats, however, phenobarbital causes minimal cytochrome P450 enzyme induction, and therefore these P450-mediated drug interactions are unlikely to occur in felines [87-88].

Phenobarbital also has clinically significant drug interactions with other anticonvulsants. Clearance of zonisamide is enhanced by co-administration of phenobarbital in dogs, possibly due to induction of CYP3A [89]. Similarly, phenobarbital increases levetiracetam (Keppra®) clearance, but by a P450-independent mechanism [90]. Phenobarbital lowers the target therapeutic concentrations of bromide needed to maintain seizure control in dogs, although this interaction is likely pharmacodynamic rather than pharmacokinetic [91]. Finally, phenobarbital undergoes autoinduction of its own metabolism, necessitating phenobarbital dosage escalations in some dogs on long-term therapy [92]. These data underscore the importance of routine therapeutic drug monitoring in any animal on phenobarbital, particularly those on combination antiepileptic drugs.

Clomipramine

Clomipramine is a tricyclic antidepressant (TCA) that inhibits norepinephrine and serotonin reuptake in the central nervous system. Pharmacodynamic interactions occur when clomipramine is combined with other drugs that increase synaptic serotonin, leading to 'serotonin syndrome' (twitching, tremor, tachycardia, myoclonic movements, hyperthermia), which can be fatal [93]. Monoamine oxidase inhibitors (MAOIs) are a well-established example in human medicine [94-96]. Although most human MAOIs are antidepressant medications, examples of veterinary MAO inhibitors include selegiline (L-deprenyl, in Anipryl®) and amitraz, found in tick dips and collars (Mitaban®, Preventic®) [93,97]. The potential for an interaction between clomipramine and these drugs has not been directly evaluated in dogs, but the veterinary clomipramine label (Clomicalm®) recommends against giving clomipramine within 14 days of either L-deprenyl or amitraz [98].

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, also inhibit neuronal reuptake of serotonin leading increased concentrations in the synapse. However, the risk for serotonin syndrome in combination with clomipramine appears to be lower than with MAOIs [99]. Other drugs that inhibit serotonin reuptake, to include tramadol and dextromethorphan (in Robitussin®), have the potential for a drug interaction with clomipramine, but the risk appears to be even lower than with MAOIs and SSRIs, at least in humans [100-101].

Clomipramine has several pharmacokinetic interactions. SSRIs can increase plasma clomipramine concentrations by inhibition of CYP2D6 in humans [47]. This can result in cardiac conduction disturbances due to the effects of clomipramine on the cardiomyocyte ion channels

and membrane potential [47-102], and ECG monitoring is recommended when clomipramine and SSRIs are combined in humans [99]. Finally, the metabolism of clomipramine can also be impaired by ketoconazole or itraconazole via CYP3A4 inhibition in humans [47], and clomipramine should probably not be combined with these azole antifungals without strong rationale and careful monitoring.

Furosemide

The loop diuretic furosemide can lead to dehydration and pre-renal azotemia, which will decrease the renal clearance of drugs such as digoxin [103,104]. Furosemide can also cause hypokalaemia and hypomagnesaemia, both of which exacerbate the cardiac toxicity of digoxin [105,106]. These interactions can lead to digoxin toxicity unless serum digoxin concentrations are monitored. In addition, furosemide enhances the nephrotoxicity of amikacin and gentamicin. Because of this, aminoglycosides should avoided in patients that require furosemide, and mannitol may be preferable to furosemide for treatment of acute renal failure caused by aminoglycosides [107]. In combination with high dosages of furosemide, ACE inhibitors can cause hemodynamic changes that can lead to acute renal failure [108]. Initial doses of ACE inhibitors should be conservative when furosemide is also instituted, and clinical status and renal function should be monitored closely, especially over the first 1-2 weeks.

Other furosemide-drug combinations can affect efficacy. Hypokalaemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine [109]. Serum potassium should be evaluated in patients with ventricular arrhythmias, and potassium supplementation should be considered if furosemide-treated patients do not respond to lidocaine. Furosemide-induced diuresis will also increase the renal loss of bromide and lower serum bromide concentrations, which may lead to seizure breakthrough [110]. The dosage of bromide may need to be increased, for example, by about 50%, in epileptic dogs for which furosemide is later added for heart failure or other disorders. Finally, non-steroidal anti-inflammatory drugs may blunt the diuretic and natriuretic effect of furosemide by impaired renal vasodilation in both dogs and humans [111-113].

Metoclopramide

As a dopaminergic (D2) antagonist and prokinetic agent, the anti-emetic metoclopramide has several important drug interactions. Metoclopramide enhances the absorption of acetaminophen [114], aspirin [115] and alcohol overdoses [116,117] in humans, via increased gastric emptying into the small intestine. Metoclopramide has also been reported to increase cyclosporine absorption in humans, but this was not demonstrated in a canine study (See Cyclosporine) [118,119]. Theoretically, metoclopramide can cause extrapyramidal side effects (tremor) when combined with phenothiazine tranquilizers [120] or SSRIs [121,122]. Tremors can also be seen at standard metoclopramide dosages in dogs with renal insufficiency, necessitating dose adjustment.

In humans, metoclopramide reduces pain on injection of propofol and decreases the amount of propofol needed for anesthetic induction (by 20-25%) by an unknown mechanism [123]. Although metoclopramide is a dopamine antagonist, it has no effect on the use of dopamine for hypotension, which is mediated by D1 receptors [124]. Interestingly, metoclopramide did attenuate dopamine-mediated renal vasodilation in dogs, but only transiently [124].

Cyclosporine

As a substrate for both p-glycoprotein and the cytochrome P450 CYP3A, the immunomodulatory drug cyclosporine has the potential for numerous drug interactions. Drugs that inhibit CYP3A decrease the clearance of cyclosporine, leading to increased blood concentrations and the potential for toxicity. These compounds include, but are not limited to, diltiazem [125], clarithromycin [126,127], ketoconazole and other azole antifungals [48,127,128], and even grapefruit juice and powder [119]. Both cimetidine and metoclopramide have been reported to decrease cyclosporine clearance in humans [118,129]. However, these drugs do not appear to significantly impact cyclosporine concentrations in dogs, perhaps due to a species difference in enzyme-substrate specificity [15,119]. The nutraceutical St. John's Wort induces CYP3A4 in humans and accelerates elimination of cyclosporine, decreasing drug concentrations; this has also been shown in dogs [130-132]. Supplements containing St. John's Wort should be avoided in dogs being treated with cyclosporine.

The interaction between ketoconazole and cyclosporine has been exploited in veterinary medicine to obtain higher blood concentrations for a given dosage of cyclosporine. This allows lower therapeutic dosages of cyclosporine and better affordability for larger dogs [49,133-135]. Recommended dosages are cyclosporine, 2.5–5.0 mg/kg once to twice

daily, depending on the disease being treated [49,133-137], and ketoconazole, 2.5 mg/kg/day [136]. Monitoring of ALT is strongly recommended during treatment, since azole antifungals can lead to increases in serum hepatocellular enzymes [138]. Trough therapeutic drug monitoring of cyclosporine (whole blood drawn just prior to the next dose) may also be helpful, but target cyclosporine concentrations have not been well established for the range of diseases treated in veterinary medicine. Extrapolating from human recommendations, several canine studies have demonstrated a clinical response by targeting cyclosporine concentrations of 400–600 ng/ml [134,135]; however, lower concentrations may be adequate for diseases such as perianal fistula and inflammatory bowel disease [139].

Both fluconazole and clarithromycin have recently been investigated for cyclosporine-sparing effects in dogs [126,128,140]. In one study,(126) clarithromycin (10 mg/kg, q 12 h) increased the area under the curve (AUC) of cyclosporine by 33%, while a second investigation [128] demonstrated a 92% increase in AUC with concurrent administration of fluconazole (4.3 mg/kg/day). Further, fluconazole (5 mg/kg/day) decreased the total daily dose of cyclosporine necessary to maintain therapeutic concentrations (400–600 ng/ml) by 39% in dogs following renal transplantation [140]. Although no direct comparisons have been performed, these data suggest that fluconazole may be a viable alternative to ketoconazole for reducing cyclosporine requirements in dogs, whereas clarithromycin may not be as effective [49,126,128].

Acknowledgements/Conflicts of Interest

Dr. Reinhart is supported by grant T32 OD010423 from the National Institutes of Health.
Dr. Trepanier has no conflicts of interest to declare.

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