

# DRUG-DRUG INTERACTIONS IN ICU

- Critical veterinary patients are predisposed to drug-drug interactions (DDI) because of the complexity of drug regimens in ICU and the number of medications used in critical patients.
- Drugs may affect the **absorption, distribution, metabolism, and/or elimination** of other drugs
- Toxicity may manifest as increased activity or loss of efficacy
- Certain pathological conditions seen in ICU patients such as hypoalbuminemia or organ failure can alter pharmacologic response

## Protein Binding

One of the most important factors in drug-drug interactions is the plasma protein concentration, specifically albumin. Albumin is the major protein responsible for binding acidic drugs such as warfarin, NSAIDS and anticonvulsants. Decreases in albumin level, which are commonly seen with critical illness, can lead to an excess of unbound, and therefore more active, drug.

Alpha<sub>1</sub>-acid glycoprotein (AAG) is the major protein responsible for binding basic drugs such as lidocaine, propanolol and amitriptyline. As AAG is an acute-phase protein, levels can increase in acute illness and therefore inhibit the actions of these medications.

## Hepatic Metabolism

Several sites for drug metabolism exists within the body; liver, kidneys, GI tract, lung and blood among others. Of these, the liver is the organ which is most important for metabolism and elimination of medications. The cytochrome P450 enzyme (actually a family of enzymes with a complex terminology), which is a lipid-membrane bound hepatic enzyme, is responsible for oxidation, hydrolysis and conjugation of drugs prior to excretion. Certain medications can either inhibit P450 (leading to increased levels of drug which are metabolized by it) or potentiate P450 (leading to increased clearance of drugs which are metabolized by it). This important enzyme system and its interactions with specific drugs are discussed in more detail below, but drugs and conditions which increase P450 activity include;

- Phenobarbital
- Rifampin
- Early sepsis (due to increased hepatic blood flow)

Conditions and drugs which decrease the activity of P450 include;

- Azole antifungals
- Cimetidine
- Metronidazole
- Omeprazole
- Trimethoprim-Sulfa
- Late sepsis
- IL-6
- Tumor Necrosis Factor- $\alpha$

## Resources

Several online and printed resources exist for comparing drugs and determining safety, although few veterinary resources are available. Human references include the drug interaction calculator available at [www.drugs.com](http://www.drugs.com) and the King Concise Guide to Critical Care Admixtures. The online drug interaction checker allows the user to select the medications that a particular patient is receiving and evaluate them for the presence of DDI. Additionally the level of threat presented by the DDI is graded from major to minor to facilitate clinical decision-making. The King Guide also makes available a wall-chart that is helpful for displaying graphical information and allows drugs to be visually compared in a matrix format.

An excellent review of the topic was published in Critical Care Medicine 2010 by Papdopolous et al; *Common drug interactions leading to adverse drug events in the intensive care unit: Management and pharmacodynamic considerations*

### Scientific studies

There is a paucity of data in human medicine, and few studies exist regarding DDI. None were identified in a search of the veterinary literature outside of a few lectures given on the topic at academic conferences. Of the few extant human studies, DDI is identified as a significant contributor to ICU morbidity; one study (Ray, Crit Care Med 2009 Suppl) identified 64% of 400 adult ICU patients as having a potential DDI, of which about 17% had a clinically relevant DDI requiring therapeutic intervention.

A 2007 study in the American Journal of Health System Pharmacology found that 7.5% of human patients admitted to ICU were there for a drug-related event and that ½ of these were for DDI.

### Specific interactions

**Metoclopramide & dopamine:** Metoclopramide is a dopamine antagonist anti-emetic commonly used in veterinary ICU settings. Dopamine is a synthetic catecholamine used to increase splanchnic blood flow (in cases of acute renal failure and pancreatitis) and as a pressor agent in hypotension. Concurrent use of dopamine and metoclopramide, which could be a common occurrence as many patients with the above conditions also experience clinically significant vomiting, could result in antagonism of the dopamine and loss of dopamine effect. Although not a particularly dangerous interaction, this is commonly encountered in ICU and clinicians should be aware of it.

**Sucralfate & quinolones:** Sucralfate is a commonly used gastroprotectant. It can form complexes with enrofloxacin in the GI tract, decreasing drug absorption. The risk is loss of efficacy of enrofloxacin. This effect may last for longer than one would think based on the dose interval of sucralfate; human studies have shown poor bioavailability of quinolone antimicrobials even 6 hours after sucralfate administration.

**Lidocaine & furosemide:** Hypokalemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine. Serum K<sup>+</sup> should be evaluated in patients with ventricular arrhythmias, and supplementation should be instituted if patients do not respond initially to lidocaine.

**Digoxin & furosemide:** Furosemide can increase serum digoxin levels. Furosemide can also cause hypokalemia, which can exacerbate the cardiotoxicity of digoxin, and pre-renal azotemia through dehydration, leading to impaired digoxin excretion. Digoxin levels should be monitored closely in patients treated with digoxin and furosemide. Renal values and serum electrolytes should be routinely evaluated during the course of therapy.

**Opioids:** Opioids are classified by their receptor affinity at any of the several known opioid receptors; most important among these are mu, kappa and sigma. Opioids that have antagonistic effects at the mu receptor, such as butorphanol, can partially reverse effects of full mu receptor agonists such as morphine and fentanyl, leading to a decrease in analgesic effect. Occasionally this interaction can be used to positive effect; in cases of dysphoria seen with full mu agonists (particularly in cats), butorphanol can partially reverse the negative effects while preserving some of the analgesic effects. The extent of this phenomenon and doses used to achieve partial reversal are a subject of some controversy.

**Tramadol & Mirtazapine:** Tramadol is an analgesic with opioid-like effects which has gained recent popularity in veterinary medicine as an agent for oral analgesia for outpatient use. Mirtazapine (Remeron®) is a tetracyclic antidepressant that has appetite stimulating properties in veterinary patients. Coadministration of tramadol with serotonin-enhancing drugs such as mirtazapine may potentiate the risk of serotonin syndrome, which is a rare but serious toxicome thought to result from hyperstimulation of CNS serotonin receptors. Symptoms of serotonin syndrome include agitation, tachycardia, hyperthermia, mydriasis, and gastrointestinal symptoms such as vomiting, and diarrhea.

**Cimetidine:** Cimetidine (Tagamet®) is a P450 enzyme inhibitor, and decreases the breakdown of many drugs as listed above. Other H2 blockers such as ranitidine and famotidine are not P450 inhibitors and should be chosen over cimetidine for ICU polypharmacy patients

**Omeprazole and clopidogrel:** Omeprazole is a proton-pump inhibitor that has seen increased use in veterinary patients for various gastrointestinal conditions. It is also a P450 inhibitor as noted above. Clopidogrel (Plavix®) is an antiplatelet agent that is sometimes used in cases of feline aortic thromboembolism and hypertrophic cardiomyopathy. It is activated to the active form by the cytochrome P450 enzyme system. If this enzyme system is impaired by concurrent administration of omeprazole, then activation of clopidogrel to the active metabolite is decreased and the risk of thromboembolic disease is increased. Substitution of pantoprazole for omeprazole or an H2 antagonist such as famotidine can be used to avoid this interaction.

*Ketoconazole and cyclosporine:* Ketoconazole is yet another P450 inhibitor, and can decrease the clearance of many drugs. This effect can be used to a therapeutic advantage with cyclosporine, which is a cyclic peptide produced by the fungus *Beauveria nivea* and is used to treat a variety of immune-mediated disorders such as perianal fistulae and immune-mediated hemolytic anemia. Administration of ketoconazole with cyclosporine will decrease the degradation of cyclosporine and increase its efficacy. This has primarily a financial advantage, as cyclosporine is often prohibitively expensive. Doses used for this protocol are;

- Cyclosporine: 4-5 mg/kg/day
- Ketoconazole 10 mg/kg/day

Cyclosporine serum levels should be evaluated at steady-state (about 1 week). The target level is 500 ng/ml until clinical remission is noted; 200 ng/ml will likely maintain remission

#### **General management guideline**

In order to minimize the occurrence of DDI's, drug regimens should be closely evaluated for all ICU patients. Each new medication added should be evaluated and screened by the clinician to screen for DDI. In critical care patients, each added drug should have a viable justification. Technicians and, if possible, pharmacists, should be involved in screening for DDI and evaluation of the drug regimen. If one is concerned about DDI, various drug references as noted above should be consulted. Knowledge of common interactions and medications involved in DDI can help the veterinary health care team avoid iatrogenic complications of therapy.

Communication is key with all team members and pet owners to screen for DDI and manage them if they occur. If a DDI is suspected or confirmed, options for management include discontinuation of the suspected offending medication, switching the medication for a similar medication or continuation of the suspected medication if the signs are not severe. Patients with suspected or confirmed DDI require vigilant monitoring and follow-up.

#### **References**

Available upon request