Drug Interactions in the ICU

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In the days of advanced veterinary care it is not uncommon to have hospitalized patients on several different oral or injectable medication. However, little is known as of yet about the interactions of complex medications on the animal's condition. With many patients being subjected to polypharmaceutical interventions drug interactions are not only possible, but likely. This presentation will seek to outline the pharmaceutical basis and definitions of an adverse drug reaction and discuss common ones in the small animal ICU setting

Adverse drug reaction terminology

Drug reactions or more appropriately termed adverse drug reactions (ADR's), occur in several different ways. An actual chemical reaction amongst two reactive substances may be one cause. A veterinary technician inadvertently administering an overdose of medication may actually be another class of ADR. There are currently seven different classifications for ADR's. Type A (augmented) ADR's represent drug reactions that occur because of known effects of the drug, but an exaggerated response in the patient. Type B (bizarre) drug reactions represent drug reactions that cannot be forseen, and those that may also have never been encountered. Type C (chronic) reactions are those that occur with long-term use of a particular drug. Type D (delayed) ADR's occur long after a drug is finished and may be hard to definitely link to the drug. Type E (end) ADR's occur when a drug is stopped suddenly and there is no withdrawal period. Type F (failure) ADR's represent the situation where drugs do not have the effect for which they were prescribed. Finally, Type G (gaffes) represent human error drug interactions; misdiagnosis, overdose or failure to administer drugs fall into this category.

Letter symbol	ADR category	Characteristics
A	Augmented	Enhanced response to drug's normal effects
B	Bizarre	Unexpected reaction (anaphylaxis)
C	Chronic	Results from long-term use of drug
D	Delayed	Reaction occurs long after drug has been stopped
E	End	Reaction occurs when drug is stopped completely
F	Failure	Reaction occurs because drug did not perform expected function
G	Gaffes	Human error

Type a (augmented) drug reactions

Type A ADR's result from exaggerated drug effects, often due to inheritable defects in the patient's ability to biotransform a drug ino an inert metabolite. Active drug circulates unchanged and can cause enhanced effects. Defects in the multi-drug resistance protein 1 (MDR-1) gene, and the p-glycoprotein system are common amongst certain breeds. In addition, there is evidence linking sensitivity to vaccines, sulphonamides, and azathioprine to inherited defects in specific enzyme systems.

Breeds documented with hypersensitivity to the above medications, or inherited defects include: Collies, Australian Shepherds, Border Collies, English Shepherds, German Shepherds, Whippets, Old English Sheepdogs, and Shelties. Drugs that utilize p-glycoprotein as a substrate (therefore potentially causing enhanced effects if the dog carries the MDR-1 gene) include: Acepromazine, Butorphanol, Dexamethasone, Digoxin, Doxorubicin, Ivermectin/Moxidectine/Selamectin, Vincristine, Mexilitine. Drugs that possibly utilize p-glycoprotein as a substrate include: ondansetron and ketoconzaole.

Breeds potentially highly suspectible to ADR's	Drugs that utilize (or possibly utilize) p-glycoprotein substrates (which could cause a reaction)
Collies	Acepromazine
Aussies	Butorphanol
Border collies	Dexamethasone
English shepherds	Digoxin
German shepherds	Doxorubicin
Whippets	Ivermectin/Moxidectin/Selamectin
Old English sheepdogs	Vincristine
Shelties	Mexilitine
	Ondansetron
	Ketoconazole

Type b (bizarre) adr's

Type B ADR's usually cannot be predicted and are hard to prevent. The typical Type B reaction is an anaphylactic/allergic or other hypersensitivity reaction. Remember the four types of hypersentivity reactions are: Type I- anaphylactic, Type II- cytotoxic, Type III- Immune complex formation and Type IV- delayed hypersentivity. Acute anaphylaxis can certainly be life-threatening and patients may show any of these clinical signs: vomiting, urticaria, erythema, angioedema, bronchospasm, hypotension, or pruritis. Type III hypersentivity reactions can also occur as a result of an ADR so drug history should be investigated in patients with immune-mediated disease involving immune-complex deposition such as polyarthropathy or glomerulonephritis. The unfortunate thing about Type B reactions is they cannot be predicted as prior exposure to the drug is NOT necessary to induce a reaction.

Potential drug interactions in the ICU

In the ICU there are several possible drug interactions that may occur. For this presentation we will discuss the following:

- Antimicrobial synergism/antagonism
- Several common drug interactions seen in small animal patients
- Recommendations for dealing with patients with hepatic and renal disease

Antimicrobial use and interactions

The co-administration of various drugs, including antimicrobials, is common in small animal patients. Many cases in a veterinary hospital will be on "triple-threat" combinations like ampicillin, enrofloxacin, and metronidazole. However, one must be aware of the known interactions between various classes of antimicrobial drugs. Synergistic reactions may be favorable and result in greater microbe death, yet antagonistic reactions may yield both drugs inert.

Synergistic reactions have been found to occur between several different classes of antimicrobials. Notably, the actions of beta-lactam and aminoglycoside enhance the killing properties of each other. In addition, synergism may also occur between fluroquinolone and any of the following: aminogylcosides, 3rd generation cephalosporins, carbapenems, or extended-spectrum penicillins. These combinations find enhanced activity against Pseudomonas, Enterococcus, Staph Aureus, and E. Coli bacterial infections. An additional synergistic combination is that of clindamycin and metronidazole. Human studies found that it was effective against Bacteriodes species. Antimicrobial antagonistic reactions are rare.

Common ICU drug interactions

How many ICU patients may be on the following drug regimen: ampicillin, enrofloxacin, metronidazole, famotidine, metoclopramide, buprenorphine, maropitant? Most likely ALL of them!

Here are some common drug interactions/reactions to be aware of.:

Drug	Effects	Drug interactions	Recommendations
Cimetidine	Inhibition of CYP-450 system	Lidocaine Theophylline Aminophylline Propranolol Benzodiazepines	• Utilize other H2 blockers (famotidine, ranitidine)
Sucralfate (ORAL)	Complexes with other drugs if administered together.	Tetracycline/Doxycycline Aminnophylline Digoxin Fluroquinolones	• Give med FIRST and follow with sucralfate 2 hours later • Most likely DO NOT need to stagger administration of Sucralfate and H2's
Ketoconazole	CYP-450 inhibitor	Variety	• Best administered at acidic pH- do not co-administer with antacids • Careful in liver failure- monitor liver function
Fluroquinolones	Can be combined in antacid/anti-ulcer medications (Calcium carbonate, Sucralfate). Also can decrease metabolism of theopylline	Theopylline	• Careful with co-administration • Monitor for side effects (tachycardia, CNS signs)

Metoclopramide	Enhances absorption of aspirin/acetaminophen (increased gastric empyting) Causes adverse effects with phenothiazines or SSRI's (like fluoxetine)	Aspirin Acetominophen Phenothiazines SSRI's	• Avoid administration with aspirin or acetaminophen ingestion • Careful with co-administration with phenothazines/SSRI's
Cisapride	CYP-3A inhibition	Azole antifungals Macrolide antimicrobials	• Arrhythmias in humans • ONLY in high doses in dogs
Furosemide	Enhances renal toxicity Decreases clearance Causes hypokalemia Increases clearance (leading to breakthrough seizures)	Aminoglycosides ACE inhibitors Digoxin Lidocaine (hypokalemia induced) Bromide	• Potentially use Mannitol for AKI • Avoid co-administration • Monitor serum K+ levels • Avoid co-administration
Omeprazole	CVP-450 inhibitor	Several Clopridogrel	• Careful with administration in liver failure • Avoid co-administration with azole antifungals • Hypercoagulability may be enhanced if administered together
Phenobarbital	CYP-450 stimulator	Glucocorticoids Ketoconazole Lidocaine Theophylline Digoxin Propranolol More	• Careful with co-administration
Dopamine	Dopaminergic effects	Metoclopramide (Dopamine antagonist)	• Avoid co-administration
Tramadol	Serotonin agonist	Mirtazapine (TCA- serotonin enhancing	• Can potentially cause serotonin syndrome

Specific concerns in critically ill patients

Protein binding

Protein binding is an important part of drug metabolism and elimination. Highly-protein bound drugs will exert enhanced effects if patients are hypoalbuminemic. Critically ill patients have many reasons to lose protein (decreased production, loss) and thus dosing should be reduced in patients with hypoproteinemia. Drugs exhibiting protein binding affinity include: NSAIDS, and anticonvulsants.

Hepatic/Renal metabolism/clearance

Patients with reduced liver or kidney function are at risk for adverse drug reactions. Free, active drug may not bind with substrates in the liver and exert enhanced effects. Metabolites, or active drug, may also not be cleared by the kidney and can cause Type A ADR's. Recommendations include: reducing doses in drugs with known hepato/renotoxicity, monitoring kidney/liver function after institution of therapy, tailoring drug regimens to each patient, monitoring patient clinical signs, educating clients on proper administration and side effects, reporting ADR's if they occur, and referring to comprehensive veterinary pharmaceutical guides (Plumb's Drug Handbook), consulting a human pharmacist, or referring to published human literature.

Polypharmacy

Human studies have found that the risk of an ADR increases each time a new drug is added to a patient's regimen. Patients should have justified reason for each drug they are on (analgesia, targeted antimicrobial therapy, immunosuppression, gastroprotectants) to increase the judicious use of pharmaceuticals and reduce the incidence of ADR's. Knowledge of the these side effects is essential when treating critically ill patients as some ADR's may be able to be prevented.

References

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