Incidence of Drug Interactions in Veterinary Critical Care Patients

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Spring, 2002

Honors Thesis
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PASS WITH DISTINCTION

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As faculty advisor for KATHERINE D LARSON

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Introduction

The critical care unit of a hospital manages the hospital’s most seriously ill patients. Ideally, a patient in a veterinary critical care unit is given drugs that are safe and effective for the condition of the animal. A veterinarian is expected to know which drugs can be used in combination without complications. Unfortunately, with the number of drugs available, and many more entering the market each year, this can be difficult. Patients are potentially exposed to clinically significant drug interactions that negatively impact the efficacy of drugs or cause further, even life-threatening, harm to the patient. In a critically ill animal, any adverse drug reaction is a concern; even a lack of efficacy of a much-needed drug can be detrimental.

Studies often disagree about the occurrence of actual drug interactions in human medicine. This is partially due to the differing effects drugs can have on each patient and the difficulty in detecting many types of interactions within the body. The risk of interactions can increase with certain conditions, such as age, genetics, disease states, and certainly the number of drugs being taken (Tatro xxvi). Dosages and indicated precautions are determined by studies that use normal, healthy animals and do not compensate for diseased or geriatric conditions, therefore the risk of adverse effects is higher for many patients than the indicated precautions suggest.

The occurrence of drug interactions in veterinary medicine has not been previously studied. The importance of checking for potentially clinically significant drug interactions before administering drugs is often understated. Most likely, a small proportion of patients are unknowingly exposed to potentially significant interactions, and this risk probably increases with the severity of the diseases affecting the animal. The purpose of the study reported here was to
determine the occurrence of potential exposure to clinically significant drug interactions and to find the average number of drugs an animal is commonly given in a critical care situation.

Background

There are three types of drug interactions; pharmaceutical, pharmacodynamic, and pharmacokinetic. Pharmaceutical drug interactions can occur before the drug is absorbed and possibly before it is administered to the patient. The interaction may occur between two drugs or between a drug and a carrier (solvent), receptacle (e.g. intravenous tubing), or the environment (e.g. administration into the gastric environment) (Ansel, 1976). Changes in pH can occur by improper dilution. The release of insulin, for example, is pH dependent, so dilution changes the rate of insulin release; a lower dilution should cause slower metabolism of carbohydrates, and would predispose the patient to hyperglycemia (high blood sugar). Ionic attractions between drugs can cause inactivation, such as between calcium and carbonate containing solutions. Drugs can also bind to receptacles. For example, diazepam binds to plastics and insulin binds to some types of glass and many plastics, creating the potential for an interaction if an intravenous line is not flushed properly between administration of drugs. The critical care environment is the most common area for interactions to occur in veterinary medicine due to the use of multiple drugs and IV administration (Boothe). Often, but not always, visible changes occur, such as discoloration, cloudiness, or the formation of a precipitate, which alert the professional to a potential problem.

Drugs administered orally can also interact to change the rate of absorption. Binding to luminal contents impairs the absorption of many drugs. Food in the stomach when the drugs are administered can alter blood flow, gastric secretions, and motility. This can change the gastric pH, which then affects the diffusion of drugs. Interactions between drugs can also prevent
absorption. Cimetidine and sucralfate should not be given concurrently with any other oral drug because they bind to and prevent the absorption of many drugs.

Pharmacokinetic drug interactions occur when one drug alters the disposition of another (Booth, Bernard), or affects the processes by which the drug is absorbed, distributed, metabolized, and/or excreted (Stockley p.4). Oral absorption occurs through the mucous membranes of the gastrointestinal tract, especially within the small intestine. The non-ionized, lipid soluble form of the drug is the form that can be absorbed. The rate and total amount of absorption depends on the pKa of the drug, its lipid solubility, and the pH of the gastric environment. The absorption can be manipulated by drug use. For example, H2- blockers and antacids both increase the gastric pH, which decreases the absorption of the antifungal ketoconazole by fifty percent (Van der Meer). Likewise, ranitidine increases the gastric pH and thus decreases the absorption of the antimicrobial drug enoxacin.

Changes in gastrointestinal motility also change the absorption by causing a change in the amount of time the drug is available at the site of absorption, such as the small intestine. Propantheline delays gastric emptying and reduces acetaminophen absorption, but increases absorption of the slowly dissolving forms of digoxin. In contrast, metoclopramide increases gastric emptying and thereby decreases absorption of digoxin because it remains in the intestine for a shorter period of time.

Pharmacokinetic interactions that affect the distribution of a drug do so while the drug is rapidly circulating through the bloodstream. Drugs can either be dissolved in the serum or bound to plasma proteins. An equilibrium is established between the bound and unbound molecules. The unbound molecules are the active drugs, whereas the bound particles are temporarily inactive, but the binding is reversible. As the active particles are metabolized or excreted, other
particles unbind to maintain equilibrium, thus becoming active. Competition occurs for binding sites to plasma proteins, most commonly albumin, or at specific tissue binding sites. The drug that successfully competes for binding depends on the affinity for the protein and the relative concentrations of the two drugs. The risk of toxicity increases if a highly protein bound drug is displaced slightly, due to a great increase in the free, active drug in the serum. If an animal were hypovolemic, meaning less blood is circulating throughout the body, blood flow would be decreased in the peripheral organs, such as in a critical care case. This can result in drug toxicity to the brain and heart, where blood flow is maintained and so the drug is concentrating.

Another type of interaction affects the metabolism or biotransformation of drugs. To prevent drugs from staying in the body indefinitely and continuing their effects, most drugs are chemically modified to a more water-soluble compound to increase excretion by the kidney. When a compound is absorbed through the intestine, the portal circulation delivers it to the liver, the primary site of drug metabolism, where the drug is chemically modified. This results in the generation of a polar compound through oxidation, reduction, or hydrolysis, or by inactivating the drugs by coupling them with another substance. The body can build up tolerance to some drugs by increasing the activity of the microsomal enzymes within the liver because these enzymes increase the rate of metabolism and excretion. These drugs begin to have less effect after prolonged use, because the increased metabolic rate of the liver results in more efficient metabolism of the drug into inactive metabolites. Phenobarbital is a very potent microsomal enzyme inducer and can enhance not only the metabolism of drug compounds, but also the hepatotoxicity of other hepatotoxic compounds (Boothe p 23). Some drugs decrease the liver’s enzymatic activity, causing concurrently administered drugs to build up to potentially toxic concentrations. Because compounds are first transported from the intestine to the liver,
increasing or decreasing the volume of hepatic blood flow will also affect the concentration of
drugs within the system. For example, cimetidine lowers hepatic blood flow, thus increasing the
amount of usable propranolol, a cardiac drug, by decreasing its modification within the liver.

Interactions can also change the effects of drugs by altering their excretion. Most
compounds exit the body in the urine or bile. These compounds are filtered from the blood as
the renal arteries course through the kidney. Small molecules diffuse across the glomerular
membrane into tubules for excretion. Large molecules, such as many drugs and proteins, employ
an active transport system to be removed. Blood flow to the kidney is controlled by renal
vasodilatory prostaglandins. Anti-inflammatory drugs such as ibuprofen can change the blood
flow by inhibiting these prostaglandins, which reduce renal excretion of lithium (a drug used for
treatment of psychiatric conditions in people), causing its serum levels to rise. Changing the pH
of the fluid within the kidney tubule, interfering with the active transport systems, or changing
the renal blood flow can alter excretion of a drug. When drugs must compete over a transport
system, greater quantities of one will be removed from the blood while the other will remain and
continue to exert its effects. Since the liver metabolizes most drugs into inactive compounds
immediately after absorption, changes in the pH of the urine affects few drugs. The pH of the
urine can; however, dictate which compounds are reabsorbed from the kidney tubules into the
bloodstream and which are excreted.

When drugs are excreted in the bile, they reenter the gastrointestinal tract and can be
reabsorbed to produce a longer effect. Oral contraceptives are one such drug. Antibiotics
dramatically reduce their effects because certain antibiotics damage the gut flora, preventing
reabsorption from occurring, thereby shortening its effects.
Pharmacodynamic interactions occur at the site of drug action, through a receptor or physiologic system, by altering the chemical or physiological response to another drug. These interactions can be either additive or synergistic to produce an increased effect, or antagonistic to decrease the effect of one or both drugs. Additive and synergistic interactions involve two drugs producing the same pharmacological effect, by similar or different mechanisms. For example, when potassium-sparing diuretics are used concurrently with potassium supplements, severe hyperkalemia may result. Some synergistic interactions are beneficial, but some can also result in serious toxicity reactions.

Antagonistic interactions involve two drugs with directly opposite pharmacological effects. For example, oral anticoagulants (which are often used in heart attack patients to prevent the occurrence of more blood clots) increase clotting time and vitamin K decreases it. When given together, the patient may lose the protective effects of the anticoagulant drug.

Antagonistic interactions can occur by interference with the drug transport mechanisms or disturbances in the fluid or electrolyte balance. Some drugs prevent the action others by blocking the receptor sites necessary for their transport, such as atropine and metaclopramide. In contrast, furosemide decreases the concentration of plasma potassium, therefore increases the sensitivity of the myocardial cells to digitalis glycosides.

Materials and Methods

How many patients are exposed to potentially clinically significant drug interactions? How many drugs are critically ill patients generally given? What systems, when affected by disease, are generally associated with an increased risk of potential drug interactions? In order to answer these questions, 801 patient records were reviewed from the small animal intensive care unit at Washington State University Veterinary Teaching Hospital, representing all cases.
admitted to the small animal ICU during the year 2000. All patients were canine or feline. The problems for which the animals were admitted or conditions otherwise noted by the veterinarians were all recorded along with the number and types of drugs they received. All drug combinations were analyzed for potential interactions. The method of administration and the time span over which the drugs were given was taken into consideration to determine if an interaction was in fact possible.

Of the interactions that were possible, a rating system was used to determine which were clinically significant. The basis for significance is the type and magnitude of effects due to an interaction, as well as the need to avoid adverse effects by monitoring patients or altering therapy. The scale used was taken from Tatro’s 2002 edition of Drug Interaction Facts. Each interaction was evaluated according to the rate of onset of the effects, the potential severity of the interaction, and the documentation available to support its clinical occurrence. With a scale of one to five, one being the most severe and five the least, only interactions that were rated as a one, two, or three in significance were included. Because this scale is used to evaluate human drug interactions, some of the drugs that are only used in veterinary medicine were not rated on this scale, but the interactions deemed significant were included.

Table 1. Classification of Drug Interaction Significance

<table>
<thead>
<tr>
<th>Significance Rating</th>
<th>Severity</th>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major</td>
<td>Suspected or &gt;</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Suspected or &gt;</td>
</tr>
<tr>
<td>3</td>
<td>Minor</td>
<td>Suspected or &gt;</td>
</tr>
<tr>
<td>4</td>
<td>Major/Moderate</td>
<td>Possible</td>
</tr>
<tr>
<td>5</td>
<td>Minor</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>
Results

Although about twenty records from the year 2000 were unavailable, 801 records were studied. Ninety-seven potentially clinically significant interactions were found, representing sixty-seven different patients. This is a twelve percent risk of potentially significant drug interactions in animals entering the small animal ICU. Animals in this study were given a mean of 3 drugs during hospitalization, but animals with potential drug interactions were given a mean of 6.39 drugs during hospitalization.

The cases with interactions were classified according to the affected system that caused their hospitalization, as shown in table 2 and figure 1. Neurology cases had thirty-six interactions, the highest number of the systems classified. Patients with cardiovascular disease were the second most likely cases to experience drug interactions (30 cases) and patients with respiratory disease followed with twenty-one cases. Patients hospitalized specifically for infectious diseases received no drug combinations with potentially clinically significant interactions.

Table 2. Potential for Interactions by Affected System

<table>
<thead>
<tr>
<th>System</th>
<th>Interactions</th>
<th># of cases</th>
<th>% interactions/system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>30</td>
<td>76</td>
<td>39.47</td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
<td>8</td>
<td>91</td>
<td>8.79</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18</td>
<td>133</td>
<td>13.53</td>
</tr>
<tr>
<td>Hematologic</td>
<td>4</td>
<td>78</td>
<td>5.13</td>
</tr>
<tr>
<td>Infectious</td>
<td>0</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>9</td>
<td>55</td>
<td>16.36</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>5</td>
<td>132</td>
<td>3.79</td>
</tr>
<tr>
<td>Neurologic</td>
<td>36</td>
<td>258</td>
<td>13.95</td>
</tr>
<tr>
<td>Poisoning</td>
<td>1</td>
<td>9</td>
<td>11.1</td>
</tr>
<tr>
<td>Renal</td>
<td>12</td>
<td>56</td>
<td>21.43</td>
</tr>
<tr>
<td>Respiratory</td>
<td>21</td>
<td>138</td>
<td>15.22</td>
</tr>
<tr>
<td>Surgery</td>
<td>11</td>
<td>248</td>
<td>4.44</td>
</tr>
<tr>
<td>Urogenital</td>
<td>9</td>
<td>72</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Figure 1. Number of Potential Interactions Per System.

* Includes endocrine/metabolic, hematologic, infectious, hepatic, musculoskeletal, poisoning, and urogenital systems.

Discussion

Figure 2. Percentage of Interactions Per System
The percentage of drug interactions according to body system classification is shown in figure 2. Patients with diseases of the cardiovascular and renal systems had the greatest percentage of potential interactions. According to these figures, cardiology cases have the greatest risk of potential drug interactions.

Phenobarbital (an antiepileptic drug) was administered with glucocorticoids in twenty-three cases. Phenobarbital decreases the therapeutic effects of glucocorticoids (dexamethasone, prednisone, methylprednisolone, and prednisolone). This occurs because phenobarbital induces liver enzymes that increase the metabolism and loss of glucocorticoids, potentially reducing their beneficial anti-inflammatory activity. The dose of glucocorticoids should be adjusted accordingly. This interaction is well documented and clinically important (Stockley p.564).

Furosemide and enalapril, or the comparable drug lisinopril, were administered concurrently eighteen times. Although these can be used together effectively, they should be monitored due to potential problems. These two drugs may cause hypokalemia, or low potassium concentration in the blood, so serum potassium levels should be monitored. Furthermore, both of these drugs can cause hypotension, increasing risk for damage to the kidneys. Three of the patients in this study developed azotemia, or nitrogen containing compounds in the blood, after receiving this combination, potentially as a result of this drug interaction.

Heparin and aspirin were used together in seven cases. The interaction between these two drugs has been well documented. They were shown to increase the risk of bleeding by two and a half times in a study of 2656 humans (Walker). This occurs because heparin suppresses normal blood clotting mechanisms, which increases bleeding times. Aspirin amplifies this by decreasing platelet aggregation (Heiden). Although they are effective in preventing post-
operative thromboembolism (a blood clot which has moved to obstruct a blood vessel), patients should be carefully monitored and all other combined use should be avoided. Enoxaparin, a low molecular weight heparin, has similar but less severe effects therefore was determined insignificant for this study.

Six cases reported concurrent oral administration of sucralfate (an ulcer medication) and enrofloxacin (a quinolone antimicrobial drug). Sucralfate reduces the absorption of enrofloxacin up to 91 percent in normal human subjects (Garrelts). The aluminum component of sucralfate may form a chelate, or chemical ring, between the cation and the quinolone to reduce its absorption. When used together, the doses of sucralfate and enrofloxacin should be well separated several hours to maximize absorption.

Phenobarbital and doxycycline (an antimicrobial drug) were administered together to three different patients. Phenobarbital reduces the serum levels of doxycycline. This anticonvulsant is an enzyme-inducing agent and may increase the clearance of doxycycline by increasing the metabolism by the liver (Stockley p.195), resulting in subtherapeutic doxycycline concentrations.

Digoxin (a cardiac drug) was administered with furosemide (a diuretic) to four patients. Although evidence is conflicting as to whether or not a reaction occurs (Stockley p 483), it is generally believed that this combination can result in digitalis intoxication. The mechanism of this interaction is not fully understood, but the cardiac glycosides, such as digoxin, inhibit the transport of sodium and potassium across the myocardial cell membranes. When certain diuretics are used, they increase the loss of potassium from these myocardial cells, which can increase the activity and toxicity of the digoxin. In these patients, serum potassium levels should be monitored or potassium-sparing diuretics, such as spironolactone, should be used.
Amphojel was used in conjunction with enrofloxacin, in three cases. When quinolone antibiotics are used with antacids containing aluminum hydroxide, such as amphojel, the result will be decreased absorption of antibiotic across the gastrointestinal membranes, or unchanged drug in the urine (Lomaestro), and decreased pharmacological effects of the antibiotic. When concurrent use cannot be avoided, administering the antacid more than six hours before or two hours after the antibiotic avoids the interaction.

Ketoconazole (an antifungal drug) was administered along with glucocorticoids to one patient. Ketoconazole reduces the metabolism and loss of some glucocorticoids by inhibiting the enzymes in the intestinal wall and liver that the drugs bind. By reducing the loss, the effects of glucocorticoids are increased. One study recommended a fifty percent reduction in the glucocorticoid dosage to compensate for this interaction (Kandrotas).

Three cases received concurrent oral sucralfate and thyroxine (thyroid hormone). An in vitro study displayed sucralfate's strong binding to levothyroxine (Havrankova). This binding would reduce thyroxine absorption in the gut. Although only one report describes this interaction in a patient, thyroxine should be taken a few hours before the sucralfate as a precaution.

Aspirin or carprofen, both non-steroidal anti-inflammatories, was administered to four patients on glucocorticoid therapy. Glucocorticoids reduce serum salicylate levels, possibly by stimulating renal filtration and thus increasing the rate of clearance. Serum levels should be monitored to ensure effective doses, especially when glucocorticoids are discontinued because serum salicylate levels can rapidly increase. More importantly, the combination also substantially increases the risk of gastrointestinal ulceration and bleeding (Carson).
Three patients were administered salicylates, such as aspirin, concurrently with antacids containing aluminum hydroxide. The serum concentration of salicylates may be reduced because the antacid increases the urinary pH, which reduces renal reabsorption of the salicylate, thus increasing urinary clearance. Although single doses of antacids will not likely be problematic, patients on chronic antacid therapy should be monitored to ensure appropriate serum levels when salicylates are administered.

Cefazolin, an antibiotic, was used in conjunction with amikacin, an aminoglycoside, for one patient. A well-documented synergistic effect increases the bactericidal activity against some pathogens (Braveny, Pascual-Lopez). Unfortunately, similar combinations of aminoglycosides and cephalosporin antibiotics are toxic to the kidneys (Cabanillas, Klastersky, Fanning). Aminoglycoside levels and kidney function should be monitored closely when using this combination.

Two patients received theophylline (a drug used for treating asthmatic patients) with phenobarbital, which induces liver enzymes dramatically. This increases the metabolism of theophylline and its removal from the body, thus greatly reducing its serum levels. When used together, assessment of serum levels and adjustment of dosages will ensure adequate therapeutic effectiveness.

Enrofloxacin was administered concurrently with theophylline. Enrofloxacin doubles the serum concentrations of theophylline and other methylxanthines, such as aminophylline, due to decreased liver metabolism. Seven of thirty-three patients in one study displayed symptoms of theophylline toxicity (Raoof). Enrofloxacin occasionally causes convulsions (Slavich), and an additive effect potentially increases this epileptogenic activity when it is combined with
theophylline. Epileptic patients should avoid use of enrofloxacin and other quinolone antibiotics, and all patients should be monitored when using this combination.

The patient given potassium-sparing diuretics and potassium supplements was at risk of a severe and life-threatening interaction. The effects of the diuretics and supplements are additive, resulting in hyperkalemia, which is abnormally high concentration of potassium in the blood. This can manifest as muscle fatigue, flaccid paralysis of the extremities, shock, electrocardiographic abnormalities and cardiac arrest. The combination should be avoided.

Aminophylline and other methylxanthines antagonize the drowsiness and mental slowness induced by diazepam, but was given concurrently in two patients. This interaction may occur if the adenosine receptors that diazepam requires are blocked by aminophylline, or if the liver metabolism of diazepam is increased (Ghoneim). This interaction may be used beneficially to reduce the effects of diazepam-induced anesthesia as it can rapidly return a patient to consciousness (Stirt), but should be used with caution.

Glucocorticoids were administered to one patient on insulin therapy, although they oppose the effects of insulin on blood glucose levels. Glucocorticoids have been shown to raise blood sugar levels and induce diabetes (David). This is antagonistic to the blood sugar lowering effects of insulin for the treatment of diabetes. Veterinarians should consider an alternate drug to glucocorticoids, or consider increasing the insulin dosage. Blood glucose should be monitored appropriately.

The combination of phenobarbital and metronidazole (an antimicrobial drug) was administered to two patients. Due to its ability to induce liver enzymes, phenobarbital greatly increases clearance of metronidazole from the body. This combination should be monitored and
a two to three fold increase in the required dosage of metronidazole can be expected when it is given in conjunction with phenobarbital.

Phenobarbital was administered with prochlorperazine to one patient. Studies have shown the concurrent administration of phenobarbital and chlorpromazine, a very similar drug to prochlorperazine, decreases the serum concentrations of both drugs 25-30% (Haidukewych, Loga). The mechanism is uncertain, but the interaction is established so patients receiving the combination should be monitored for decreases in serum concentrations.

One patient received digoxin, a digitalis glycoside, while also on thyroid therapy. Patients with hyperthyroidism are relatively resistant to digitalis and hypothyroid patients are very sensitive to it (Huffman, Croxson). As treatment proceeds and the thyroid therapy begins to take effect, hypothyroid patients may need their digitalis dosage increased slightly, and hyperthyroid patients may need their dosage of digoxin reduced.

Butorphanol was administered with hydromorphone to one patient. Butorphanol is a \( \kappa \) agonist and a \( \mu \) antagonist. Hydromorphone is a \( \mu \) agonist. Because they have opposite effects, the use of these drugs in combination will cause a decrease in the efficacy of both.

A high percentage of patients in this study were exposed to potentially significant adverse drug interactions. However, not all interactions reported here were unknown to the clinician. If the proper precautions were taken, many of these combinations could be useful. In some situations, potential drug interactions must be considered in light of the diseases being treated. In some patients, the risk of harming the patient is greater if drug therapy is withheld than if two potentially interacting drugs are administered. In other situations, an alternative drug can be administered, avoiding the potential drug interaction but maintaining effective therapy for the patient. Whether such factors were considered in each of these listed interactions was not
evaluated. However, it is important to note that all of the interactions included in this study carry the potential for significant adverse effects.

The same drugs are often given to patients with similar diseases, such as patients with intervertebral disk disease. Many similar cases come through WSU’s Veterinary Hospital because of the availability of many veterinary specialists, and a 24-hour intensive care unit. Therefore, the drugs used to treat patients included in this study may be somewhat dependent on the diseases and prescribing practices of veterinarians at WSU. Whether or not the incidence of drug interactions would be similar in ICU patients at other veterinary teaching hospitals is unknown.
Bibliography


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