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DRUGS AND THE KIDNEYS: PREVENTING AND MANAGING THEIR POTENTIAL ADVERSE EFFECTS

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INTRODUCTION

The kidneys receive a higher percentage of the cardiac output (20%) than most organs and have a high metabolic requirement than many other organs. The kidneys are also a major route of drug excretion, which exposes the kidney tubules to high concentrations of drugs and drug metabolites. Drug-induced renal disease is classified according to the area affected: 1) glomerular nephritis, 2) tubular necrosis, 3) interstitial nephritis, and 4) obstructive nephropathy.

DRUGS THAT PRESENT A RISK TO THE KIDNEYS

There are many drugs that may injure the kidneys. Among those that are used in veterinary medicine, we are concerned about: aminoglycoside antibiotics, tetracyclines, amphotericin B, cyclophosphamide (Cytoxan), non-steroidal anti-inflammatory drugs (NSAIDs), cisplatin (Platinol), cyclosporine, and radiographic contrast agents.

AMINOGLYCOSIDES

Aminoglycoside antibiotics (eg, gentamicin, amikacin, tobramycin, kanamycin) have been the drugs most studied with respect to drug-induced nephrotoxicity. Aminoglycosides preferentially concentrate in the cells of the proximal tubules, reaching the tubular cells from the luminal side. Uptake into the proximal tubular cells is saturable, so exposure to a high concentration is not necessarily more toxic than a lower one. However, persistent concentrations over the course of several days, will increase the risk of nephrotoxicity. When aminoglycosides enter the proximal tubular cells, they disrupt electrolyte and water regulation in cell membranes, and the drug accumulates within lysosomes (myeloid bodies). Proximal tubular dysfunction is the result of impairment of organelle function.

The risk factors that contribute to aminoglycoside nephrotoxicity include: a) prolonged aminoglycoside therapy: > 7 to 10 days, b) electrolyte depletion (K^+, Na^+), c) volume depletion, and d) pre-existing renal disease. One review of predisposing factors (Brown et al, 1985) found that most small animal cases of gentamicin-induced nephrotoxicity had received the drug for an average of 6.8 days, the dosages were greater than 2 to 4 mg/kg every 6 to 8 hours; the diagnosis was based largely on azotemia and rule-outs of other causes. Most patients had normal renal function before gentamicin was administered. However, animals with previous renal function impairment are at a greater risk for toxicity (Frazier, et al, 1988).

The diagnosis of aminoglycoside nephrotoxicity is made on the basis of a history of nephrotoxic drug administration and clinicopathological signs of renal failure (polyuria, azotemia, and enzymuria). The management of toxicity entails supportive care. In many patients, aminoglycoside injury can be reversed if the problem is recognized early enough. To support the patient one should employ fluid diuresis to decrease azotemia and uremic signs and maintain electrolyte balance. However, fluid diuresis will not increase the clearance of aminoglycosides from the body, it will only produce a more dilute urine.

To prevent neprhrotoxicity from aminoglycosides, the most important preventative measure is to ensure that the patient has healthy renal function prior to drug administration. Since it is unlikely that glomerular filtration rates (GFR) – or a surrogate measure of GFR such as creatinine clearance – will be measured prior to drug administration, the most consistent parameter that will predict a risk of nephrotoxicity is the ability to concentrate urine and the serum creatinine level. If these parameters indicate reduced renal function, aminoglycoside therapy should be done cautiously, if at all.

Alternatively, therapeutic drug monitoring can be used to predict aminoglycoside drug clearance and measurement of drug concentrations can predict drug-induced toxicosis. This can be determined by obtaining at least two plasma samples at least one hour after drug administration. If drug elimination is found to be slow, reduced clearance should be suspected, which increases the risk of kidney injury.

Our current method of administration for aminoglycosides is to administer them once a day. This has reduced the risk of nephrotoxicosis from aminoglycosides because it reduces the exposure to the kidneys. Common dosages used are: gentamicin 10-15 mg/kg for dogs, and 5-8 mg/kg for cats; amikacin 15-30 mg/kg for dogs, and 10-14 mg/kg for cats. (All doses listed are IV, SC, or IM). Since drug uptake into the proximal tubular cells is independent of the concentration in the tubule, a high dose given once a day is less likely to injure the kidneys than smaller doses given more frequently.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

The kidney is an active site for prostaglandin production. Prostaglandins play a role in tubular function as well as vascular tone. Healthy animals are somewhat immune from adverse effects from NSAID (Lobetti and Joubert, 2000), but if there is renal compromise (eg, dehydration, tubular dysfunction, electrolyte depletion, anesthesia, etc), the kidney is dependent on cyclooxygenase 1 and 2 (COX-1 and COX-2) for prostaglandin synthesis to autoregulate water metabolism, tubular function, and renal blood flow (Gambaro & Perazella, 2003). Renal toxicity associated with NSAIDs is characterized by decreased renal perfusion, sodium and fluid retention, and decreased renal function. In people, pain in the kidney area has been recorded. NSAID-associated renal injury is associated with inhibition of renal prostaglandins, which are involved in the maintenance of renal hemodynamics and sodium and fluid balance. When NSAIDs are administered (eg, flunixin, phenylbutazone, ibuprofen) prostaglandin synthesis is inhibited and renal ischemia can result (Gunson et al, 1983; Rubin 1986; Clive and Stoff, 1984). The combination of anesthesia and NSAIDs may increase the susceptibility to renal injury (Mathews, et al, 1990). In most cases, NSAIDs at recommended doses are safe to animals with healthy kidneys. However, animals with renal disease are more at risk for dehydration, which can increase the likelihood of NSAID-induced nephropathy. In healthy animals, COX-2 inhibiting drugs have been safe, even for animals undergoing anesthesia (Boström et al, 2002; Lobetti et al, 2000), but there is no data available from administration of COX-2 inhibitors to animals with compromised function. One should not assume that NSAIDs that are more specific for the COX-2 enzyme are not necessarily safer for the kidneys. Both COX-1 and COX-2 enzymes are involved in renal blood flow regulation and tubular function. According to

the manufacturer's data, even deracoxib, which is highly COX-2 selective in dogs, produced renal lesions at high doses. (Dose-dependent renal tubular degeneration / regeneration in some dogs at 6, 8, and 10 mg/kg treatment.)

Chronic analgesic nephritis: There is another form of analgesic nephritis, usually caused by chronic use of acetaminophen (eg, Tylenol) in people. This syndrome has not been described in domestic animals.

ALLERGIC NEPHROPATHY

Renal injury can be caused by an allergic reaction, most often to antibiotics (eg, penicillins, cephalosporins, sulfonamides). The occurrence of this adverse reaction is not very well documented in veterinary patients. When it occurs, the reaction often is delayed because it usually requires at least 5 to 7 days for signs of this reaction to appear after initiation of drug therapy. The reaction appears to be caused by a type III hypersensitivity reaction and may be associated with other systemic signs of allergy. Allergic reactions may produce either glomerular injury or interstitial nephritis.

OBSTRUCTIVE NEPHROPATHY

Obstructive nephropathy has been most often associated with the administration of sulfonamides. Crystals of sulfonamides can form in the renal tubules causing crystalluria. Sulfonamides are more likely to precipitate in urine when the urine is acid, but usually this reaction requires high doses. The acetylated forms of the drug (especially sulfadiazine) are the least soluble. This is a rarely-reported problem with the current use of sulfonamides. (Since dogs do not have the ability to acetylate sulfonamides, this may be less likely in this species.)

AMPHOTERICIN B

Amphotericin B (*Fungizone*) is a polyene macrolide antibiotic which has a high rate of nephrotoxicosis. Early reversible nephrotoxicosis is seen with each daily dose, but permanent nephrotoxicosis is related to the total cumulative dose. Assessments of renal function should be carefully monitored throughout treatment. It may become necessary to abandon therapy with amphotericin if there is persistent azotemia.

Nephrotoxicity is less if patients are pre-treated with fluid therapy (NaCl) and receive the infusion at a slow rate (over 4-6 hrs). A commonly cited dose for therapy is a test dose of 0.25 mg/kg for the first treatment, then 0.5 mg/kg administered every other day until a total cumulative dose of 4 to 8 mg/kg has been given. Some references have suggested doses of 1 mg/kg for each dose to increase efficacy. The total cumulative dose is limited by nephrotoxicosis. To decrease risk of nephrotoxicity, several approaches have been used:

Malik and coworkers (1996) have reported on the administration of amphotericin B subcutaneously . In their report, amphotericin was administered to dogs and cats SC diluted in 0.45% saline and 2.5% dextrose at cumulative doses of 8-26 mg/kg. Except for local irritation, injections were well-tolerated and higher doses were administered without producing azotemia as compared to the IV route.

Use in lipid emulsion: Intralipid 10% is used as a diluent for amphotericin B and infused IV (Lamothe 1999; Cortadellas 2004). Add 50 mg amphotericin B in 10 ml sterile water to an additional 30 ml sterile water and 10 ml of a lipid solution (both Intralipid 10% and 10% soybean oil have been used). After vigorous shaking doses from 2 to 2.5 mg/kg have been given IV.

Lipid commercial formulations have been used in people but have not gained widespread use in veterinary medicine due to their high cost. The advantage over the traditional formulation is that they are less toxic. The can cost as high as $300-500 per day! (See review by Plotnick, 2000). Formulations available include: amphotericin B lipid complex (ABELCET), amphotericin B cholesteryl sulfate complex (Amphotec), and liposomal complex of amphotericin B encapsulated in a lipid bilayer (AmBisome).

The advantage of these lipid and cholesteryl formulations of amphotericin B is that, in comparison to the conventional formulation of amphotericin B (amphotericin B deoxycholate), these can be given at higher doses to produce greater efficacy with less toxicity. (Hiemenz and Walsh, 1996) Doses of lipid complex formulations of amphotericin B have been 3 mg or more per kilogram, compared to 0.25 to 0.5 mg/kg of the conventional formulation (Walsh, et al. 1999). Decreased toxicity is attributed to a selective transfer of the lipid complex amphotericin B, releasing the drug directly to the fungal cell membrane and sparing the mammalian cell membranes. Reduced drug concentrations in the kidneys, and diminished release of inflammatory cytokines from amphotericin lipid complex compared to conventional formulation also may prevent adverse reactions.

MANAGING PATIENTS WITH RENAL DISEASE

For drugs that are cleared by the kidneys, drug dose rates should be altered when there are documented decreases in creatinine clearance or elevations in serum creatinine. For a drug that relies on the kidneys for drug clearance (Cl_R) a loss in renal function will proportionately decrease drug excretion. That is, a 75% loss in renal function results in a 75% loss in renal drug clearance.

Dosage adjustments can be made from estimates in the loss of renal function. The most exact method of assessing renal function is to measure creatinine clearance (Cl_{CR}), which is an estimate of GFR. The decrease in the patient's Cl_{CR} compared to a healthy animal can be used to either adjust the dose interval, or the dose as follows:

Constant interval, decreased dose method:
$Dose_{Renal\ Failure} = Dose_{Normal} \times (Patient's\ Cl_{CR}) Normal\ Cl_{CR})$
Constant dose, increased interval method (τ = dose interval):
$T_{Renal\ Failure} = T_{Normal} \times (Normal\ Cl_{CR}) Patient's\ Cl_{CR})$.

Alternatively, a less precise method is to make a dose adjustment based on serum creatinine: $Dose_{Renal\ Failure} = Dose_{Normal}$ (In this example, the patient's creatinine should be in units of mg/100 mL.) Because serum creatinine is relatively insensitive to changes in creatinine clearance (Finco, et al 1995), this method is only a rough approximation and assumes that serum creatinine in healthy animals is 1.0 mg/100. The method of relying on serum creatinine is less reliable when creatinine levels are high (eg, above 4 mg/dL). An estimate of dose adjustment using serum creatinine is more risky in geriatric compared to younger animals because serum creatinine is affected by animal's muscle mass. A geriatric animal with low muscle mass and poor renal function may have a falsely low serum creatinine.

ANTIMICROBIAL SELECTION TO PATIENTS WITH RENAL DISEASE

In patients with renal disease, antibiotic selection is challenging. Avoid tetracyclines, and aminoglycosides. However, doxycycline is safe because it is eliminated by non-renal routes. The drugs that rely on metabolism for their elimination can be used cautiously. This includes macrolides (erythromycin, azithromycin) and clindamycin. Avoid metronidazole because the most common adverse effect is CNS toxicity and this may be difficult to distinguish from problems caused by uremia.

For other drugs there is always a concern that, in a patient with reduced renal function there may be decreased renal clearance and a need to adjust dosages. For example, some fluoroquinolones accumulate in human patients with renal compromise (Fillastre, et al 1990), but others such as ciprofloxacin do not. When marbofloxacin was administered to dogs with renal impairment, there was no significant effect on drug disposition and no need for dose modification. (Lefebvre et al 1998) Renal failure had only a minimal and biologically irrelevant effect on marbofloxacin disposition in the dog. Apparently, other routes of drug clearance can play a role in elimination when renal function is compromised.

All beta-lactam antibiotics carry a risk of accumulation in patients with impaired renal function. This includes penicillins, ampicillin, amoxicillin, and cephalosporins. The most common adverse effects from accumulation is CNS toxicity (eg, tremors, seizures) or gastrointestinal (vomiting). If a ß-lactam is considered reduce dose frequency if any signs of toxicity are observed. One of the extended-spectrum cephalosporins, cefotaxime, cefpodoxime axetil, ceftazidime, or cefotetan is a good choice if the patient has a serious gram-negative infection. All except cefpodoxime must be injected. If there is persistent azotemia the frequency of administration should be decreased in proportion to the decrease in renal function. One of the signs of accumulation of β-lactam antibiotics in renal failure are gastrointestinal problems (vomiting, nausea), or neurological signs, such as seizures. (Chow et al, 2004; Wallace 1997). For serious resistant infections, the carbapenems can be considered. Of those available, meropenem (Merrem) may be considered. It is not associated with neurotoxicity that is seen with imipenem accumulation.

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