



Adverse Drug Reaction and Nephrotoxicity Caused By Commonly Used Antibiotics in Dogs

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Abstract Drug-induced kidney disease constitutes an important cause of acute renal failure and chronic kidney disease. Drug-induced nephrotoxicity refers to kidney damage induced by medication administered for the purpose of diagnosing or treating another medical disorder. It is more commonly recognized in dogs. And although drug-induced nephrotoxicity may occur in dogs of any age, older dogs are more susceptible. The kidney is an organ susceptible to the injurious effects of the drugs because of its functional properties. Understanding the mechanisms of nephrotoxicity enables the planning of preventive strategies. Antibiotic associated renal failure is predominantly noted with the use of aminoglycoside antibiotics though it may also occur with beta-lactam, vancomycin, sulfonamides and antifungal antibiotics. Aminoglycosides are very often associated with nephrotoxicity, ototoxicity and neuromuscular blockage. An adverse drug reaction (ADR) is a serious concern for practicing veterinarians and other health professionals, and refers to an unintended, undesired and unexpected response to a drug that negatively affects the patient's health. It may be iatrogenic or genetically induced, and may result in death of the affected animal. So, in this prospective review, we attempt to bring forth the commonly occurring adverse drug reactions, antibiotics induced nephrotoxicity, underlying mechanism, and the treatment & prevention.

Keywords Adverse Drug Reaction, Nephrotoxicity, Dogs

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: glomerular nephritis, tubular necrosis, interstitial nephritis and obstructive nephropathy [1].

Nephrotoxicosis can be induced by the administration of pharmacologic agents (or drugs), which interfere with the blood flow to the kidneys as well as cause tubular dysfunction in the kidneys. If left untreated, the damage to the renal tubule cells may lead to tubular necrosis and even kidney failure. Risk factors that may increase the odds of developing drug-induced nephrotoxicity include dehydration, advanced age, and fever. On the other hand, there may be a significant number of interactions that occur only in the species we are treating in pet and companion animals. Some of the most commonly prescribed anti-microbial agents and reported to have toxic effects in dogs are described. Moreover, drug-induced nephrotoxicity may even lead to chronic kidney disease months or years later. Therefore, if any signs of illness -- such as vomiting or diarrhea -- recur, contact your veterinarian immediately [2].

Drugs induced nephrotoxicity in dogs

A. Antibiotics induced Nephrotoxicity in dogs

The veterinarians and other health professional commonly encounter inter-individual variations in response to drug administration. Some patients respond well to a particular therapy, while others fail to demonstrate idiosyncrasy. Often, small animal clinicians are informed by the dog owners or breeders that their dogs are sensitive to a particular type of medication. This variation in drug response among individuals is due to the varied genetic make-up which



explains the adverse drug reactions and offers a major step towards safe pharmacotherapy. Therefore, pharmacogenetics has been used to explain idiosyncratic drug reactions in veterinary patients. The genotype specific approaches to therapy in childhood (GATC), a national Adverse Drug Reaction (ADR) network, has been established in Canada in 2005 to report specific ADRs in children and identify the predictive genomic biomarkers of drug risk and thus, to provide a framework of ADR surveillance. Adverse drug reactions (ADRs) are associated with serious harmful effects and may lead to death in both human and animal patients [3]. A recent study in Turkey revealed that maximum cases on ADR in animals were reported from antibacterials (26%). The most observed adverse drug reactions were anaphylaxis and the local reactions at the injected site [4]. Several plant-based medicinal products have been evaluated for ameliorating the toxic effects, even after ADR reported following administration of anticancer drug, cisplatin [5].

B. Causes, Symptoms, mechanism of action and diagnosis

Sulphonamides

The sulphonamides such as sulfamethoxazole, sulfadiazine, sulfadimethoxine have been reported to cause numerous dose-dependent reactions in dogs including haematuria, non-regenerative anemia, interfered thyroxine synthesis, erythema multiforme, erythema nodosum, photosensitivity, urticarial rashes and many other skin diseases. The mechanism and time course of these reactions vary considerably from species to species. Anaphylaxis may not accompany the initial cutaneous drug reactions, but re-exposure can exacerbate this life-threatening reaction. These are immediate type immune-mediated reactions due to presence of IgE antibodies against the sulfonamide [6]. Binding specificity studies suggest that the 5-methyl-3-isoxazolyl group on sulfonamides is an active component in antibody recognition. Such reactions occurring across a spectrum of sulfonamides in a given dog is suggested from cross-reactivity within a variety of sulfonamides. Fever together with a morbilliform or maculopapular, non-urticarial skin rashes are generally manifested by 7-14 days post initiation of therapy with sulfonamide. Bioactivation of sulphonamide may result from formation of metabolite protein conjugates as inferred from studies demonstrating the ability of reactive metabolites of sulfonamides to bind covalently to proteins. This implies that the slow acetylator phenotype patients are at a greater risk of toxicity as they bioactivate a larger fraction of the administered dose cytochrome P [7].

Penicillin: Penicillin and its derivatives are the common cause of ADR which vary from a morbilliform eruption to anaphylaxis. Ampicillin and amoxycillin are most commonly implicated in morbilliform drug reactions. The high cutaneous reaction rate may be attributed to the diacyl side chain of these compounds that gives rise to the formation of linear polymers. Acute generalized exanthematouspustulosis is commonly caused by β -lactam and macrolide antibiotics. Histological section demonstrates an intraepidermal spongiform pustule with eosinophils. The incidence of true cross-reactivity between penicillins and cephalosporins is poorly recorded. Still, the patient's owners are often advised against fatal anaphylaxis while administering cephalosporin to pets with a history of penicillin allergy [8]. However, since 1980 the degree of cross-reactivity between penicillin and current-generation cephalosporins has been found to be less than 5%. In such cases of β -lactam allergy, penicillin skin testing is advised [9]. Carbapenem is also restricted in penicillin allergy due to the evidence of cross reactivity between other antibiotics and penicillin. In such situations, aztreonam (Azactam) is safely administered because of extremely rare cross-reactivity [10].

Penicillin for dogs is prescribed for infections of the urinary tract, lungs, and kidneys. Resistance to it mostly encountered when the drug administration is stopped before the prescribed course is completed, thus prompting a chance for the infection to return. Atopical penicillin lotion or ointment may be prescribed for various skin infections in dogs and also sometimes used in treating leptospirosis, wounds, and dental infections. In dogs and cats, penicillin-V is administered @5.5-11mg/kg b wt at every 6-8 hour interval. It is not used in animals hypersensitive (allergic) to penicillins or -lactam antibiotics such as cephalosporins. Penicillins can cross the placenta, and hence, is not advised in pregnant animals although no detrimental results to fetuses have been reported [11].

Cephalosporin

The penicillin and cephalosporin are -lactam antibiotics structurally characterized by a five-membered thiazolidine ring and a six-membered dihydrothiazine ring respectively. Risk of adverse cutaneous reaction to cephalosporins in a patient with a history of penicillin allergy is controversial, but becomes visible to be quite low. Both cephalosporins and the penicillins have been implicated in inducing a pemphiguslike syndrome [12]. The same syndrome is also induced by thiol drugs including captopril, D-penicillamine, and gold sodium thiomalate which is characterized by flaccid bullae clinically indistinguishable from pemphigus vulgaris that develop within the first few weeks of drug therapy. Direct immunofluorescence demonstrates IgG antibodies targeting the keratinocyte desmosomal components desmoglein I or III. Cephalosporin also induces the onset of gastrointestinal disturbances, hemolysis and glycosuria in dogs. Renal damage and ototoxicity have been linked to repeated aminoglycoside administration or its overuse. The renal damage ranges from mild, subclinical changes to more severe nephrotoxicity



and acute renal failure [13]. The animal's ability to improve depends on the nature of medication exposure and the quantity of healthy renal tissue remaining to compensate [14]. Neomycin is considered as the most nephrotoxic while aminoglycoside, dihydrostreptomycin and streptomycin are least nephrotoxic, and the other common aminoglycosides are considered somewhere intermediate between those three drugs in their toxicity.

Aminoglycosides

Aminoglycosides cause nephrotoxicity by accumulating in the proximal tubular cells and interfere with cellular metabolism and transport processes by establishing lysosomal phospholipid complexes [15]. These tubular changes can progress to proximal tubular necrosis with increasing exposure to the drug. The toxic renal changes caused by gentamicin and other aminoglycosides lessen the elimination of the antibiotic and augment serum antibiotic concentrations, thereby increasing the potential toxicity. Dogs with subclinical renal dysfunction are more sensitive to the toxicity of gentamicin and develop oliguria and acute renal failure that may not be reversible from a high gentamicin dose. The local renin-angiotensin system is activated leading to local vasoconstriction causing a decrease in the glomerular filtration rate. The increase in plasma creatinine (sCr) level due to reductions in glomerular filtration rate is used as the suggestive measure of nephrotoxicity. The detectable elevation in sCr and/or BUN precedes mRNA expression products in urine and/or kidney that could be used as potential biomarkers for acute gentamicin related nephrotoxicity in dogs. Nephrotoxicity is exacerbated by many other factors that compromise renal blood flow. Co-administration of certain drugs including furesomide, ethacrynic acid, cyclosporin, cisplatin, and vancomycin (but not teicoplanin) have been reported to increase the risk of nephrotoxicity [16].

Some aminoglycosides are more likely to cause auditory toxicity (cochlear ototoxicity) and others are more likely to cause vestibular ototoxicity. This may be due to the distribution characteristics of each drug and its ability to concentrate in each sensory organ and result from damage to the sensory hair cells in the cochlea and the labyrinth. Unlike nephrotoxicity, auditory or vestibular toxicity is often irreversible. A rare form of auditory toxicity after single dose administration of aminoglycosides has been described to be associated with two different mutations in the mitochondrial 12S ribosomal RNA gene. Neuromuscular paralysis is very rare as compared to the nephrotoxic and ototoxic effects of aminoglycosides. The neuromuscular blocking effects of dihydrostreptomycin, gentamicin, neomycin, and streptomycin have been demonstrated with the dose rate of 14-43 mg/kg. The postsynaptic blocking component of this effect can be reversed by a cholinesterase inhibitor, such as neostigmine and the apparent presynaptic effect can be antagonized by the administration of calcium. Besides, tetracycline causes A-Colitis-X in horses, drug fever in cats, and photosensitivity in grazing animals [17].

Aminoglycosides are not used in animals hypersensitive (allergic) to aminoglycosides and are also not prescribed in anaerobic bacterial infection. Aminoglycosides is contraindicated in dogs used for hearing sensation very frequently to perform their work as the vestibular impairment is often irreversible. Gentamicin therapy is also contraindicated in nephrotoxicity, neuromuscular disorders and in pregnancy or nursing animals. Renal damage in older dogs and heartworm microfilaria infection, hypovolemic dehydration are often the predisposing factors for aminoglycoside toxicity. It is highly advised to monitor the renal function during the course of treatment mostly through urinalysis indicate early nephrotoxicity. The nephrotoxicity of aminoglycoside is checked by adjusting the drug dosing rate and duration of therapy, which under no circumstance should be more than the recommended dose in plasma. It is always commended to avoid concurrent or sequential use of nephrotoxic, ototoxic, or neuromuscular blocking drugs, particularly other aminoglycosides because of their additive effects [18].

Concurrent administration of furosemide with aminoglycosides may enhance nephrotoxicity. Diuretics should not be employed together with aminoglycosides as it increases the risk of kidney damage. Products causing hearing loss, vestibular disease, or kidney disease should not be recommended along with aminoglycoside therapy in order to shy off further complications. The possibility of neuromuscular blockade and respiratory paralysis exists if aminoglycosides are given to patients receiving anaesthetics, neuromuscular blockers, or massive transfusions of citrate-anticoagulated blood. Calcium salts may reverse neuromuscular blockade if it occurs. The management of toxicity entails supportive care. 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 [19].

Fluoroquinolones

Fluoroquinolones are an important group of antibacterial agents widely used in veterinary practice in the treatment of infectious diseases. It mostly causes arthropathy in young animals, retinal degeneration in cats, neuromuscular paralysis in horses. Young and growing pups are most prone to quinolones induced arthropathy especially on



weight-bearing joints, the underlying mechanism of which still remains obscured [20]. Quinolones have an inhibitory effect on DNA, collagen and proteoglycan synthesis and on the generation of oxygen derived reactive molecules [21-22]. Irreversible chondrotoxicity and tendinitis associated with quinolones may also be explained on account of their chelating properties for bi- and tri-valent ions mostly magnesium ions, leading to formation of free radicals or due to an altered functionality of integrin receptors on chondrocyte and tenocytes surface. Tendons cannot easily compensate these altered functions because of their poor vascularization. Apoptosis of the tendon and chondron cells, a consequence of altered α_1 integrin receptors and Map-kinase pathway is the final event in the pathogenesis of fluoroquinolone-induced tendinopathies as evidenced by cultured human tendon cell line. The findings that quinolone-induced damage on connective tissue is partially due to magnesium chelation also support the observation that patients with a latent magnesium deficiency could be at an increased risk of tendon disorders [23].

Chloramphenicol, a powerful broad spectrum bacteriostatic drug, is most often administered in dogs with pneumonia, infection of the brain, eye, and in anaerobic infection. Toxic adverse effects of chloramphenicol include bone marrow depression, gastrointestinal upsets, hypersensitivity reactions and gray baby's syndrome. All dogs do not experience side effects while taking chloramphenicol but puppies unable to digest and process chloramphenicol the same way an adult canine can thus resulting in toxic accumulation of the chloramphenicol in the puppy's body. Chloramphenicol crosses the blood brain barrier and reaches onto the foetus, and is, therefore, contraindicated in pregnant bitch. Chloramphenicol is rarely associated with blood dyscrasias where the drug targets the bone marrow. Gray baby's syndrome in neonates and infants occurs due accumulation of unconjugated chloramphenicol in the body that blocks electron transport system in liver, myocardium and skeletal muscle, and is characterized by vomiting, hypothermia, ashen gray cyanosis, cardiovascular collapse and sometimes leading to death. The animal neonates are deficient in microsomal enzymes and inadequately metabolize the drug. Several diagnostic tests and therapy are being practised to ameliorate drug hypersensitivity and ADRs. Laboratory tests including skin testing radioallergosorbent test (RAST) are conducted to study IgE mediated immune reaction with therapeutic interventions of antihistamines, systemic corticosteroids and bronchodilators. Similarly, direct or indirect Coombs' test is carried out to read the cytotoxic immune reaction. Patch test or lymphocyte proliferation assay is performed to learn the delayed and cell-mediated immune reaction and the present drug therapy is stopped with administration of antihistamines and topical or systemic corticosteroids [1, 15].

Macrolide antibiotics

Do not produce serious toxic effects in animals but tylosin and tilmicosin have tendency to produce cardiovascular toxicity. Very high doses and prolonged use in human and animals cause untoward effects namely, transient auditory impairment and superinfection. Oral erythromycin may be highly irritating to the stomach and when given by injection may cause severe phlebitis. The combination of some macrolides and statins used for lowering cholesterol is not advisable and can lead to debilitating myopathy. This is because some macrolides (clarithromycin and erythromycin, not azithromycin) are potent inhibitors of the cytochrome P system, particularly of CYP A [24]. Macrolide antibiotics: Lincosamide antibiotics preferred bacteriostatic antibiotics in dermatological problems in veterinary practice. They are well absorbed orally and penetrate well into infected skin and affects the bacteria including staphylococci. Rapid development of bacterial resistance and occasional gastroenteric upset are the main disadvantages for their use. Decreased milk production and ketosis are also common due to toxicity of lincosamide antibiotics in milch cows. It also causes loose stools in dogs and pigs, vomiting in cats, and Pseudomembranous colitis in human, horses and other herbivores respectively. However in some animals, adverse effects have been noticed with parenterally administered lincomycin. An early detection of the cause of ADR and prompt treatment of anaphylaxis are essentially required for successful management. Acute therapy in emergency is directed toward oxygenation and maintenance of normotension. The most appropriate therapy includes the use of epinephrine, oxygen, vasopressors, corticosteroids and adequate fluid replacement. ADR needs to be differentiated from other symptoms to avoid the discontinuance of the necessary drugs [25].

A complete and thorough knowledge of drugs causing immunologic reactions, patients' history of allergy if any and mastery over use of satisfactory alternatives against hypersensitivity is a must. Adverse reaction can be minimized through use of established protocols for premedication or through desensitization achieved with graduated dosage schedules. A number of sulphonamides and their combinations are being used to treat respiratory, urinary tract, skin, or gastrointestinal infections in veterinary practice. However, it is contraindicated in pregnant or nursing animals, dehydrated animals and in those animals suffering from bladder or kidney stones, liver or kidney diseases. The pet should be encouraged to drink plenty of water to prevent crystalluria formation in the kidneys. Similarly, adequate drinking water should be provided to dogs with routine monitoring of blood cell abnormalities during sulphonamide administration [26].



When drug-induced nephrotoxicity is suspected, a veterinarian will often biopsy a portion of kidney tissue. This will help him or her identify kidney failure and also the proper course of treatment. Another useful diagnostic procedure is a urine analysis.

C. Treatment & Prevention

Most dogs with drug-induced nephrotoxicity will require inpatient care, especially those that are also suffering from kidney failure. In these severe cases, surgery may be required. Once the dog has returned to your home, it is important that his activity be reduced and that you provide him with a modified diet that is not excessive in protein and phosphorous. Dehydration is a common threat for dogs with kidney problems; you will need to monitor him for any untoward symptoms and advise your veterinarian if they should occur, who may assist by administering fluid therapy. Electrolyte panels may be performed as frequently as every one or two days in order to evaluate the severity of azotemia, a condition commonly associated with drug-induced nephrotoxicity, in which abnormal levels of nitrogen-containing compounds (such as a number of body-waste compounds) are found in the blood. This is of utmost importance, as dogs with severely progressed azotemia may develop acute kidney failure within days. Among the other main approaches used so far to reduce or to protect against aminoglycoside nephrotoxicity, the most consistent effects have been observed with the use of antioxidants and especially deferoxamine. On the basis of the finding that gentamicin forms complexes with mitochondrial Fe^{2+} to catalyze the formation of free oxygen radicals iron chelators were tested and were proven to be effective in the prevention of aminoglycoside-induced ototoxicity. Extension of this finding to nephrotoxicity appears to be possible, but biophysical and biochemical considerations suggest that the protective effect of deferoxamine may be critically dependent on the dosage of gentamicin. Other compounds were also used on account of their antioxidant effects, but the mechanisms have not always been unambiguously established. Means of protection based on a correction of the functional abnormalities or on an increase in cell regeneration capabilities have also been attempted, but no clinical application has so far been made [27-30].

Polyaspartic acid has emerged as a very successful protectant against aminoglycoside-induced nephrotoxicity from the screening of various polymers that are likely to impair the binding of aminoglycosides to kidney membrane vesicles. In experimental studies with animals, the coadministration of polyaspartic acid with gentamicin or amikacin was shown to protect against the development of phospholipidosis and phospholipiduria, as well against all early and late signs of aminoglycoside nephrotoxicity. Actually, both polyaspartic acid and the aminoglycoside reach the lysosomes by endocytosis and form ion-pair complexes within these organelles due to the acidic pH prevailing therein. *In vitro* studies demonstrated that polyaspartic acid prevents aminoglycoside binding to negatively charged phospholipids bilayers and thereby makes the drug unable to inhibit the activities of lysosomal phospholipases [31].

Further studies showed that polyaspartic acid also protects against gentamicin-induced alterations of phospholipid metabolism in cultured cells and of electrophysiological alterations in cultured human proximal tubular cells. Polyaspartic acid also prevents impairment by gentamicin of homotypic fusion of renal cell endosomes and blocks the process of aminoglycoside-induced aggregation of negatively charged liposomes, all events which had been directly related to the binding of gentamicin to phospholipids. *In vivo* studies have now defined the limits and the duration of the protection afforded by polyaspartic acid [32].

Moreover, pharmacokinetic evaluations have shown that polyaspartic acid increases the penetration of gentamicin in the so-called deep peripheral compartment (which most likely represents the intracellular drug-polyaspartic acid complex and which suggests that the antibiotic is stored in a nontoxic form). A protective effect of polyaspartic acid against ototoxicity has also been demonstrated. A movement toward large-scale toxicological studies and clinical applications of polyaspartic acid therefore appears to be warranted but is still hindered by the lack of a clear definition of the precise type of polymer which needs to be used. It must indeed, at the same time, be filtratable through the glomerulus, bind effectively to gentamicin, remain sufficiently stable in the kidney to afford significant protection, and not causing renal toxicity per se, as was shown for polymers that are too stable [33-34].

Daptomycin (LY 146032), which contains three Asp residues, also colocalizes in the lysosomes of the renal cortex with gentamicin and protects against lysosomal alterations *in vivo*. *In vitro*, it increases the negative charge density of membranes, while at the same time affecting the lipid packing, two effects which counteract those of gentamicin and facilitate the access of the catalytic site of the phospholipases to their lipidic substrate. Torbafylline (HWA-448), an analog of the vasoactive agent pentoxifylline, also protects against gentamicin-induced phospholipidosis, but its mode of action is unknown [35-36].

The best way to prevent this type of toxicity is to not use nephrotoxic drugs. However, if your dog requires this type of medication, administer it only under the advisement of your veterinarian. You should also consult him or her before adjusting the dosage and the possibility of adverse drug interactions.



Conclusion

Among nephrotoxic agents, the most common offenders are drugs prescribed for the treatment of clinical conditions not directly concerned with the kidney. In this category, antibiotics are major inducers of kidney disease. While the incidence of nephrotoxicity mediated by allergic responses is uncommon, high frequencies of renal impairment occur with the administration of the major antibiotic used to combat systemic fungal infections, amphotericin B, and the aminoglycosides used to combat broadly antibiotic resistant organisms such as *Pseudomonas aeruginosa*. A detailed picture is beginning to be established of the pathological alterations which arise in the kidney upon antibiotic administration. A few of the circumstances which may potentiate antibiotic-induced nephrotoxicity are known, but it is unclear why in the same kidney some nephrons are damaged while others are not when presumably exposed to similar local concentrations of the drug.

ADR or drug toxicity is a common problem that threatens the safety and health status of the patients, but as the whole represents burden on the whole health care system. It is often poorly diagnosed and documented in day to day medical practice. The diagnosis of ADR and mechanisms involved are also often hardly studied and understood by the unskilled practitioners, and they attribute these symptoms to the progress of the disease. The first step in managing ADR or toxicity is to discontinue the causative medication and its substitution with alternative medications having unrelated chemical structures. In majority of patients, symptoms usually resolve within two weeks. Systemic corticosteroids speed up the recovery and use of topical corticosteroids and oral antihistamines improve the dermatologic symptoms. Elucidation of the key players in mediation of ADRs will provide therapeutic targets for its management and prevention.

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