IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Adverse Drug Reactions and Drug Interactions Associated with the Use of Antibacterial Agents in Veterinary Patients

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Abstract: An adverse drug reaction is an unwanted, toxic effect of a drug that encountered at usual therapeutic dosages. The intensity of such reactions ranges from minor complications to serious life-threatening conditions or even death of the individual. Despite selective toxicity, antibacterial agents can produce harmful effects and contribute a large portion of drug-associated untoward reactions. Some antibacterials like chloramphenicol, aminoglycosides, tetracyclines, fluoroquinolones etc. exhibit different adverse reactions, especially in hepatic and renal diseases. Examples of adverse drug reactions include hypersensitivity reactions (penicillins), superinfections (tetracyclines) and direct tissue toxicity viz. aminoglycoside induced nephrotoxicity, tetracyclines induced hepatotoxicity, fluoroquinolones associated arthropathy, chloramphenicol associated bone marrow suppression and so on. The adverse reactions do not remain constant with all the patients but vary according to the genetic makeup of an individual. Similarly, drug interaction due to combination therapy further may increase the possibility and magnitude of adverse drug reactions. This review is an effort to bring forth commonly encountered adverse drug reactions and drug interactions associated with various antibacterial drugs in veterinary practice.

Keywords **- Adverse drug reaction, antibacterial agents, drug interactions, combination therapy, toxicity, veterinary practice.**

I. INTRODUCTION

Antibiotics have been extensively used in human as well as veterinary medicine throughout the world mainly for the therapeutics and prophylaxis of infectious diseases [1]. Recently, the use of antibiotics in veterinary practices has increased dramatically with an annual global consumption more than 6000 tons which is almost double that of human use [2]. Antibiotics are substances derived from microbes and microbial products that kill or inhibit the growth of other microorganisms. All antibacterial agents are not antibiotics, because some are synthesised solely through chemical procedures, e.g. sulphonamides and fluoroquinolones [3]. Although, antibacterials have selective toxicity towards bacteria their use is associated with inherent risks of developing serious harmful effect or even death in both human as well as animal patients [4,5].

The statements of Napoleon Bonaparte (1820), “I do not want two diseases; one nature made, one doctor made” and that of Matthew Prior (1714), “Cur’d yesterday of my disease, I died last night of my physician” highlight the adverse effects exhibited by the drugs [6]. In the United States, the patients admitted to the hospital due to adverse drug reaction contribute to about 8% of total hospital admissions [7]. Generally, the maximum number of cases of drug-induced adverse reactions are from antibacterial agents [5,8]. Similarly, when antibacterials are combined with or administered successively with certain drugs, may lead to increased chances of development of untoward effects [9]. So adverse reactions and drug interactions associated with the antibacterial agents are reviewed in this article.

1.1 TERMINOLOGIES AND DEFINITIONS

a) Selective toxicity

It is the ability of a chemotherapeutic agent to selectively kill an invading microorganism without harming host cells [9].

b) Toxic effect

The effect which occurs as an exaggeration of the desired therapeutic effect due to administration of the drug at higher doses or prolonged time than therapeutically required [10].

c) Side-effect

The unwanted but unavoidable minor reactions that occur at normal therapeutic doses, which are predictable and usually dose-related [6].

d) Adverse drug reaction

Harmful or seriously unpleasant effects occurring at therapeutic doses and which call for a reduction of dose or withdrawal of the drug and/or forecast hazard from future administration [6].

e) Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation or expected from characteristics of the drug [10].

f) Serious adverse effect

Any untoward medical occurrence that at any dose results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/incapacity or is life-threatening [10].

g) Adverse event/adverse experience

It is an untoward occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment [10].

h) Idiosyncratic reactions

These are abnormal, unexpected, or peculiar reaction seen in only certain patients. For example administration of sulphonamides in patients with glucose-6-phosphate dehydrogenase deficiency results into haemolytic anaemia [11].

i) Iatrogenic effect

The adverse reactions which are produced unintentionally by physicians in their patients [11].

j) Drug interaction

A drug interaction is a situation in which one member of a class of drugs alters (either decrease or increase) the intensity of the pharmacological effects of another drug given concurrently [12].

II. ADVERSE DRUG REACTIONS (ADRS)

It is a general consideration that if a drug is effective in producing a pharmacological effect, it may produce untoward or adverse effects too [7,10]. Therefore, medical as well as veterinary practitioners commonly encounter ADRs in their patients, which may vary individual to individual due to the varied genetic make-up [4]. The intensity of drug-induced untoward effects ranges from minor health complications to serious life-threatening conditions or even death of an individual. These effects occur upon individual sensitivity of animals and can be a consequence of known toxicity of the drug or of individual or idiosyncratic reaction [8].

According to WHO, the ADR is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modifications of physiological function [13]. In the scenario of veterinary medicine, ADR is an unintended or unexpected effect on animals, human beings or the environment, including injury, sensitivity reactions or lack of efficacy associated with the clinical use of a veterinary drug including pharmaceutical, biological and pesticide products [12]. The terms “adverse reaction” and “adverse effect” are almost synonymous, except that an adverse effect is related to the drug and an adverse reaction to the patient. But both terms are different from an “adverse event”. An adverse event is a harmful happening that occurs during exposure to a drug without any assumption being made about its cause [6].

In veterinary practice, ADRs are mainly associated with vaccines, antimicrobial drugs, non-steroidal anti-inflammatory drugs, ectoparasiticides, anthelmintics and anaesthetic agents [12]. Antibacterial induced ADRs include hypersensitivity reactions (penicillins); superinfections (tetracyclines, penicillins) and direct tissue toxicity like nephrotoxicity (aminoglycosides), hepatotoxicity (tetracyclines, macrolides), cardiotoxicity (macrolides) neonatal arthropathy (fluoroquinolones), bone marrow depression (chloramphenicol) neurotoxicity (nitroimidazoles, fluoroquinolones) and so on [9].

2.1 IMPORTANT AETIOLOGIES OF ADRS

In general, the causes of ADRs include off-label use of medicines, excessive dosage, prolonged duration of treatment, owner's negligence or unfamiliarity with the drug and proper drug handling and accidental ingestion in high doses [7]. However, some of the important aetiologies of ADRs are as below [6].

a) Inherent Anomalies

The reactions resulting from hypersensitivity or idiosyncrasy including those due to genetic factors, physiological variables like age, sex, gestation etc.

b) Acquired Patient abnormalities

It includes the reactions due to the presence of associated disease which may modify the resultant response to the drug.

c) Anomalies of Drug Presentation and Administration

The reactions which are developed as a result of over-dose, changed bioavailability characters, inappropriate route of administration and medication error.

d) Drug Interactions

The effects produced due to the combined effects more than one drug administrated at the same time.

2.2 CLASSIFICATION OF ADRS

The ADRs are mainly classified into two categories as type A and type B [4,15]. However, other minor categories have also been proposed, which do not encounter commonly in veterinary practice [9,12,16].

a) Type A (augmented/ dose-related)

These are dose-related adverse reactions occurring frequently as an exaggeration of normal therapeutic or expected drug response. Type I reaction are predictable and can be avoided by a practitioner who is familiar with the drug and the patient. For example the nephrotoxic effect of aminoglycosides.

b) Type B (bizarre/ non-dose-related)

These type of reactions are not related to the drug concentration or dosage. Further, these are unpredictable, seen only in susceptible individuals hence generally are unavoidable. Examples of type II ADRs include drug allergies (penicillins) or idiosyncrasies.

c) Type C (chronic/ dose-related and time-related)

The continuous reactions associated with long-term use of drugs which primarily include drug dependence.

d) Type D (delayed/ time-related)

It includes delayed reactions for example, nitrofurazone and metronidazole induced carcinogenesis, metronidazole-associated mutagenicity and tetracycline induced teratogenicity

e) Type E (withdrawal/ end-of-treatment)

These reactions include adrenocortical insufficiency following the withdrawal of glucocorticosteroids, withdrawal syndromes following discontinuation of treatment with benzodiazepines or β-adrenoceptor antagonists and iatrogenic diseases like fluoroquinolone induced cartilage damage in young ones.

f) Type F (treatment failure)

There are numerous reasons for the failure of the treatment.

Similarly, drug reactions can be classified further into immunologic and non-immunologic etiologies. The majority of ADRs are caused by predictable, non-immunologic effects and some are caused by unpredictable effects that may or may not be immune-mediated while a few reactions constitute true drug hypersensitivity [4,17].

III. PRECAUTIONS AND CONTRAINDICATIONS OF ANTIBACTERIAL AGENTS

The antibacterial-induced adverse effects aggravate in certain physiological and/or pathological conditions of animals; similarly certain species or breeds of animals are more prone to specific antibacterial-induced ADRs. Therefore, those antibacterials are contraindicated or should be used with extreme precautions in the situations where their ADRs get augmented. In general all the antibacterials should not be administrated in the patients with known history of hypersensitivity associated with the respective drug. Particularly, β-lactams are contraindicated in patients hypersensitive to any of the β-lactam antibiotic. Fluoroquinolones and macrolides can produce QTc-prolongation hence should be cautiously used in cardiac patients particularly those receiving class III or class IA antiarrhythmic drugs. Similarly, sodium and potassium salts of penicillin G should be avoided in patients with congestive heart failure. Chloramphenicol and oxazolines are contraindicated in hematological disorders, pre-existing blood dyscrasias or myelosuppression. Nitrofurans are contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency due to risk of extravascular hemolysis. Penicillins, quinolones, nitromidazoles and polypeptide antibiotics should be used cautiously in patient with pre-existing CNS disorders. Fluoroquinolones, tetracyclines, amphenicols and

lincosamides are contraindicated in young, growing patients. Chloramphenicol and tetracyclins should not be administrated to patient receiving or scheduled to receive vaccines as it may result into vaccination failure due to immunosuppression. Tetracyclines and ceftriaxone should not be mixed with IV fluid like ringer lactate (RL) and Ca-preparations. Outdated tetracyclines may cause severe damage to the PCT of nephron hence better be avoided. Aminoglycosides should be avoided in patients with renal failure, ear diseases (mainly with ruptured tympanic membrane), working dogs are used for hearing sensation, diseases characterised by muscle weakness viz. milk fever and myasthenia gravis.

As far as route of administration is concerned, penicillins and tetracyclines should not be injected through intrathecal route while rapid IV infusion of tetracyclins (mainly in horses) and glycopeptides should be avoided. With regards to the breeds and species, tetracyclins should be avoided in Doberman breed of dog, while tilmicosin (macrolide antibiotic) should be avoided in pigs and prolonged use of cephalosporins should be avoided in cats. Because of high risk of gastrointestinal upset and superinfection, use of antibacterials like penicillins, macrolides, lincosamides, tetracyclins should be avoided in monogastric herbivores (horse, rabbits, gerbils, guinea pigs, hamsters) [3,9,22].

3.1 Liver and Kidneys – Principle Organs Predisposed to ADRs

Liver and kidneys receive a higher percentage of blood and are capable of drug concentration, hence are the most vulnerable organs to drugs induced reactions [15]. The liver plays a crucial role in drug disposal by drug metabolism as well as elimination. Hence, the liver disease may increase the susceptibility of untoward drug reactions as a result of altered pharmacokinetics of the drug [14]. Antibacterial drugs such as erythromycin, amoxicillin-clavulanate, nitrofurantoin, minocycline and sulphonamides are known to cause drug-induced hepatotoxicity [18,19]. Similarly, the kidneys also are the major organ involve in the drug excretion. Some drugs themselves are nephrotoxic and exacerbate renal diseases. Therefore, it is not surprising that kidney diseases frequently provoke ADRs especially when renal excretion contributes importantly to the elimination of a particular drug or its metabolite [5,14]. Many antibacterial drugs require close monitoring in renal disease. Aminoglycosides being nephrotoxic are best avoided when possible in renal disease [20]. Some of the antibacterial drugs which should be avoided or used cautiously in renal or hepatic diseases have enlisted in table 3.2.1.

Table 3.1.1: Antibacterials to be avoided or used cautiously in liver and kidney diseases [12]

	Liver disease	Kidney disease
Antibacterials to be avoided	Chlortetracyclines, erythromycin estolate, sulphonamide-trimethoprim	Aminoglycosides
Antibacterials to be used cautiously	Chloramphenicol, lincosamides, macrolides, metronidazole, sulphonamides, tetracyclines	Fluoroquinolones, lincomycin, nalidixic acid, naficillin, tetracyclines (except doxycycline), nitrofurantoin, sulphonamide-trimethoprim, sulphonamides

The penicillins and carbapenems accumulate readily in renal disease and can be associated with neuromuscular toxicity, myoclonus, seizures, and coma. Therefore, serum drug concentrations of such antibiotics should be monitored and doses and intervals should be adjusted accordingly [20]. The decrease in drug disposal either by reduced metabolism or excretion or both, extend drug retention in plasma causing cumulative dosing and increases the potential for ADRs. In patients with hepatic and/or renal diseases some drugs need the adjustment of dose or interval to avoid toxic effects. We have mentioned some examples regarding dose and interval adjustment of antibacterial drug in patients with renal diseases, in table 3.2.2.

Table 3.1.2: Dose/ interval adjustment of antibacterial agents in renal diseases [20]

Dose/ interval adjustment	Antibacterial agents
Interval extension: Drug to be repeated every 8h can be given every 12 h, in moderate renal disease Drug to be repeated every 12h can be given every 24h, in severe renal disease	Cefazolin, cefepime, cefotaxime, cefoxitin, cefpodoxime, ceftazidime, ceftizoxime, cefuroxime, cephalexin, meropenem, sulfamethoxazole, trimethoprim, vancomycin, amoxicillin, ampicillin/sulbactam, ticarcillin, piperacillin, enrofloxacin, tetracycline
Dose reduction: 100% of the dose should be decreased to 75% with moderate renal disease and down to 50% with severe renal disease	Cefixime, amoxicillin/clavulanate, ticarcillin/clavulanate, erythromycin, metronidazole, piperacillin/tazobactam, penicillin G, ciprofloxacin, enrofloxacin, rifampin,
Do not require dose adjustment	Azithromycin, chloramphenicol, clindamycin, dicloxacillin, nafcillin, penicillin VK, doxycycline, linezolid, minocycline

Further, some antibacterial agents can be replaced with other having an alternative route of excretion, so that delayed elimination can be avoided. For example, doxycycline will be preferred over other tetracyclines in renal impairment because it is mainly excreted through bile [20,21]. Similarly, antibacterials like aminoglycosides, sulphonamides and quinolones should be avoided in dehydrated patients and particularly latter two are contraindicated in patients with acidic urine [9].

3.2 LACTATION AND PREGNANCY- RISKS FACTOR FOR ADRS

In a broader sense, antibiotics with higher milk penetration or which are unsafe or contraindicated in neonates are not suitable to be used in milk-producing and nursing animals. The antibacterials which should be avoided in lactating animals include fluoroquinolones, chloramphenicol and sulphonamides. On contrary, antibacterials considered to be safe in milch animals include the aminoglycosides (oral bioavailability is very low), macrolides, penicillins and the cephalosporins. Metronidazole though is safe in neonates, the mutagenicity and carcinogenicity limit their use in lactating animals [8]. Similarly, penicillins, cephalosporins and macrolide antibiotics are generally considered safe in pregnancy. While antibacterial agents like tetracyclines, sulphonamides and aminoglycosides are known to cause toxic effects in developing foetus, therefore, should better be avoided in pregnancy. The antibiotics like chloramphenicol, fluoroquinolones and others have not been proved to be safe in pregnancy, hence, should only be used when the benefits of therapy clearly outweigh the risks [9,22,23].

IV. DRUG INTERACTIONS

As mentioned earlier, drug interaction can occurs when a drug alter the effect of other through various mechanisms when given simultaneously. Drug interactions include pharmaceutical, pharmacokinetic, pharmacodynamic, direct chemical or physical interactions; interactions in gastrointestinal absorption (alteration of gastric pH, formation of complex, alteration in gastric emptying time); competition for protein-binding sites; interactions at receptor sites; interaction due to accelerated metabolism; inhibition of metabolism; alteration of renal excretion and alteration of pH or electrolyte concentrations. Many of these drug interactions usually lead to increased risk of ADRs [11,12].

It is a general concept that the combination of two bactericidal drugs (e.g. penicillin G and streptomycin) or two bacteriostatic drugs (e.g. sulphamethoxazole and trimethoprim) often result in increased antibacterial activity while combination of bactericidal and bacteriostatic drug (e.g. enrofloxacin and nitrofurantoin; penicillin and chloramphenicol) usually results in antagonism and reduced antibacterial response. However, this rule has some exceptions for example, combination of bactericidal streptomycin and bacteriostatic tetracycline in treatment of brucellosis, and ceftriaxone (bactericidal) combined with azithromycin (bacteriostatic) in treatment of enteric fever produce synergistic antibacterial effect. Similarly, combination of bacteriostatic chloramphenicol with other bacteriostatic agents e.g. macrolides or lincosamides (similar mechanism of action) leads to decreased antibacterial activity [9]. Some of the common antibacterial-associated adverse drug reactions and drug interactions encountered in animals have been summarized in table 4.1.

Table 4.1: Common adverse reactions and general drug interactions encountered in veterinary patients with the use of antibacterial agents [3-5, 9, 20, 22, 24-35]

S.N.	Common Adverse Drug Reactions	General Drug Interactions
1.	**Penicillins**	
	• Relatively non-toxic except hypersensitivity • Hypersensitivity: anaphylaxis, rashes, urticaria, drug fever, angioedema, serum sickness, vasculitis, • GI disturbances: diarrhoea, nausea, vomiting, anorexia • Superinfection (mainly in PG-fermenters) • Thrombocytopenia • Neurotoxicity: seizure, ataxia • Nephrotoxicity: interstitial nephritis • Cation toxicity (due to Na/ K- penicillin G)	• Bleeding disorder with anticoagulants due to ↓ vit. K synthesis • Salicylates, sulphonamides, phenylbutazone displace penicillins from plasma proteins • Probenecid blocks tubular secretion competitively & ↑ $t_{1/2}$ of penicillins • Chloroquine ↓BA of ampicillin following oral co-administration
2.	**Cephalosporins**	
	• Relatively non-toxic • Hypersensitivity (similar to penicillins but comparative less frequent) • GI disturbances: nausea, vomiting, diarrhoea • Superinfection • Nephrotoxicity: interstitial nephritis (mainly due to cephaloridine) • Hepatitis • Thrombocytopenia & neutropenia • Pain at IM injection site	• Potentiation of nephrotoxicity by co-administration of aminoglycosides, colistin & loop diuretics • ↓bactericidal action by bacteriostatic agents (e.g. CAP) • Probenecid blocks tubular secretion competitively & ↑ $t_{1/2}$ of cephalosporins
3.	**Aminoglycosides**	
	• Nephrotoxicity: neomycin> tobramycin> gentamicin are most toxic while dihydrostreptomycin least toxic. • Ototoxicity: usually irreversible; cats are most susceptible (neomycin, amikacin, kanamycin are ototoxic while streptomycin> gentamicin are most vestibulotoxic) • NM blockade: muscular weakness, apnoea, respiratory arrest (neomycin & streptomycin are potent NM blockers followed by kanamycin & amikacin; while gentamicin & tobramycin are causes least NM blockade)	• ↑ nephrotoxicity with simultaneous use of diuretics (furosemide, mannitol), cisplantin, cyclosporine & vancomycin while diuretic additionally ↑ototoxicity • ↑ risk of NM blockade & respiratory paralysis when used with inhalant anaesthetics, other NM blockers or massive blood transfusion with citrate as anticoagulant
4.	**Quinolones**	
	• Arthropathy: cartilage deformities & joint growth disorders in young ones • GI disturbances: vomiting, diarrhoea • CNS disorders: dizziness, CNS stimulation, convulsions • Nephrotoxicity: crystalluria in acidic urine (mainly in dog) • Retinotoxicity: acute blindness in cats receiving enrofloxacin	• Co-administration with polyvalent cations, antacids, sucralfate, multivitamins & mineral supplements causes malabsorption of FQs • Co-administration of corticosteroids specially in old aged cause rupture of achilles tendon

	• Embryotoxicity • Hypersensitivity and photosensitisation • Neuromuscular paralysis in horses • Haemolytic anaemia • *Torsade de* pointes: prolongation of QTc • Superinfection (with *Cl. difficile* & MRSA)	(tendinitis); also ↓seizure threshold • Chelation of polyvalent cations (Al, Fe, Mg, Zn, Ca etc.) • FQs ↓ metabolism of theophylline and caffeine • Probenecid reduces renal excretion of FQs • Nitrofurantoin antagonizes FQs
5.	**Tetracyclines**	
	• GI disturbances: irritation, pain, diarrhoea, anorexia, oesophageal strictures • Superinfection: candidiasis, enterocolitis, pseudomembranous colitis • Osteo-dental toxicity: Inhibition of calcification (hypoplastic dental enamel); permanent tooth discolouration (yellowish followed by brownish); delayed fracture healing; suppression of foetal & neonatal bone growth. • Hepatotoxicity: fatty infiltration & jaundice) • Nephrotoxicity (mainly due to outdated & incorrectly stored preparations) • Nephrogenic diabetes insipidus (due to demeclocycline) • Photosensitization & pigmentation of nails • Urolithiasis in dogs after log-term therapy • Hypersensitivity: angioderma, anaphylaxis • CVS toxicity: Hypotension, collapse & sudden death with rapid IV infusion (associated with vehicle); thrombophlebitis, prolong blood coagulation • Elevation of intracranial pressure particularly in young ones • Fanconi syndrome: Glucose, amino acids, uric acids, phosphates & bicarbonates are passed into urine instead of their reabsorbed • ADH antagonism: demenocycline causes syndrome of inappropriate ADH <u>Long-term use</u> • leukocytosis, atypical lymphocytes, toxic granulation of granulocytes & thrombocytopenic purpura	• Antacids, polyvalent cations (Al, Ca, Mg Fe etc.) saline purgatives, kaolin, pectin & sodium bicarbonate ↓ absorption of TCs (except doxycycline & micocycline) • Co-administration with nephrotoxic drugs (e.g. methoxyflurane) ↑nephrotoxicity • Interfere with bactericidal activity of βLs & AGs • Aggravation of bleeding with concurrent use of oral anticoagulants (↓ prothrombin activity & ↓ vit. K synthesis) • Microsomal enzyme inducers (e.g. phenytoin, phenobarbital) ↓ $t_{1/2}$ of TCs • Tetracyclines may produce raised levels of digoxin & lithium
6.	**Sulphonamides**	
	<u>Acute Toxicity</u> • Nephrotoxicity: cystalluria, haematuria, UT obstruction; (dehydration & acidic urine enhances the toxicity) • Blood dyscrasias: rare but fatal; (haemolytic anaemia) • Hypersensitivity: rashes, exfoliative dermatitis; (sulpadiazine may result into reversible immune-mediated sterile polyarthritis in Doberman dogs) • GI disturbances, hepatitis, risk factor for acute pancreatitis • Excess salivation (cats with foam at mouth receiving oral sulphonamides) • CNS disorders: ataxia, convulsions, collapse <u>Chronic toxicity</u> • Hypovitaminosis-K: hypoprothrombinaemia, bleeding disorder; (mostly seen in poultry with sulphaquinoxaline) • Kiratoconjunctivitis sicca (KCS): i.e. dry eyes, (mostly seen in dogs, associated with sulphadiazine, sulphamethoxazole & sulphasalazine) • Bone marrow suppression: anaemia, granulocytopenia, thrombocytopenia. • Hepatic necrosis: associated with potentiated sulphonamides (due to accomolation of sulphadehydroxylamine, the hepatotoxic metabolite) most commonly seen in dogs (due to slow acetylation) • ↓ carbonic anhydrase enzyme: causes acidosis; thin shelled eggs in poultry Thyrotoxicosis: High doses for 3 weeks causes decreased iodization of colloid & decreased concentration of thyroxin & thyronin (reverse back to normal after 3 weeks of discontinuation of therapy).	• ↑ effect of oral anticoagulants, methotrexate, sulphonylurea, tolbutamide, thiazides & uricosuric agents (by displacing from plasma albumin) • Indomethacin, probenecid displace sulphonamides from plasma proteins • Local anaesthetics like procaine (releases PABA); vit. B-complex (folate, vit. B_3) & amino acids (glutamate, methionine) antagonize action of sulphonamides • Ca & antacids ↓ oral absorption • Gelatine, albumin, peptone, serum protein etc. bind with sulphonamides and interfere with their activity. • Presence of pus or tissue breakdown products neutralizes the activity of sulphonamides • Antifolate activity & $t_{1/2\ of}$ phenytoin is increased by sulphonamides hence ↑ their toxicity • When given in combination of cyclosporin, risk of nephrotoxicity is increased • Sulphonamides inhibit the carboxylation of tolbutamide.
7.	**Amphenicols**	
	• Bone marrow depression: Aplastic/ hypoplastic anaemia; pancytopenia; (associated only with CAP not with florfenicol or thiamphenicol) • Reversible, dose-dependent, non-regenerative anaemia • Dose-independent irreversible anaemia • GI disturbances:diarrhoea, anorexia & malabsorption syndrome in neonates • CVS toxicity: collapse, haemolysis & death in large animals (rapid IV infusion) • Hypersensitivity: rashes & fever in pets • Immunosupression • Gray-baby syndrome: characterised by vomiting, hypothermia, flaccidity, ashen grey cyanosis, cardiovascular collapse & death of newborn. • Hepatic microsomal enzyme inhibition (irreversible)	• Co-administration with MLs & LCSs (Compete for 50S ribosomal subunit) • Inhibits hepatic CYPs hence ↑$t_{1/2}$ of warfarin, phenytoin & tolbutamide • Co-administration of phenobarbital or rifampin induce CYPs hence ↓ $t_{1/2}$ of CAP • Cyclophosphamide potentiates bone marrow depression • Interfere with bactericidal activity of βLs & AGs • Contaminant use of anticoagulants ↑ bleeding tendency (↓ vit. K synthesis, ↓metabolism of anticougulants)

	• Hepatotoxicity & neurotoxicity in pigs • Jarisch-Herxheimer reactions may occur when used for syphilis, brucellosis & typhoid fever	• IV CAP given with cimetidine causes fatal aplastic anaemia
8.	**Macrolide antibiotics**	
	• Relatively safer except tilmicosin • GI disturbances: vomiting, diarrhoea, anorexia, regurgitation, epigastric pain (following oral administration; horses are most susceptible) • Erythromycin stimulates GI motility by acting on motilin receptors • Hypersensitivity: Rashes, fever, skin eruptions • Cholestatic hepatitis: erythromycin estolate & telithromycin • Cardiotoxicity: Erythromycin, clarithromycin, telithromycin, tilmicosin & tylosin cause tachycardia, fibrillation • *Torsade de pointes*: prolongation of QT (erythromycin & clarithromycin) • Superinfections • Pain at the site of injection • Rectal edema & partial anal prolapse in swine with the use of erythromycin	• ↓ activity when combined with LCSs or CAP • Erythromycin & toleandromycin inhibits hepatic CYPs hence ↑ $t_{1/2}$ of carbamazepine, theophylline, warfarin & methylprednisolone • In acidic environment activity ↓ • Antacids ↓ absorption of azithromycin from gut • Anticoagulant effect of nicoumalone & warfarin ↑ by MLs due to inhibition of metabolism • Prolongation of QT when used with cisapride
9.	**Lincosamides**	
	• Do not produce serious toxic effects • GI disturbances • Superinfections: pseudomembranous colitis (mainly in horses) • ↓ milk production & ketosis in cattle • Skeletal muscle paralysis • Hypersensitivity and pain at the site of injection	• ↑ NM blocking effect of local anaesthetics & skeletal muscle relaxants • Co-administration with MLs & CAP (compete for 50S ribosomal subunit) • Antagonizes the effect of neostigmine & pyridostigmine
10.	**Nitrofurans**	
	• GI disturbances (nausea, vomiting, diarrhoea) • Neuropathies & CNS disorders (excitement, convulsion, peripheral neuritis) • Depression of spermatogenesis • Ocular disturbances • Hepatitis, cholestatic jaundice • Poor weight gain • Carcinogenicity (in laboratory animals) • Hypersensitivity • Brownish discolouration of urine	• Antacids containing magnesium salts ↓absorption of nitrofurans • Antagonizes the antibacterial effect of FQs (*in vitro*) • Inhibit MAO so should not be given with other MAO-inhibitors like TCAs, buspiron & sympathomimetics • Uricosurics ↓clearence of nitrofurantoin hence ↑ $t_{1/2}$ as well as toxicity
11.	**Nitroimidazoles**	
	• GI disturbances (anorexia, vomiting, diarrhoea) • Excessive salivation in cats receiving metronidazole • Neurological disorders (tremor, ataxia, lethargy, nystagmus, disorientation, head tilting, seizures) • CVS disorders (neutropenia, haematuria, bradycardia) • Teratogenicity • Mutagenicity & carcinogenicity (in laboratory animals)	• Increases the effects of oral anticoagulants • Metronidazole ↓ metabolism of phenytoin but phenobarbital ↑metabolism of metronidazole • Antacids reduce absorption of imidazoles • Cimetidine increases metronidazole concentrations & toxicity
12.	**Carbapenems**	
	• GI disturbances: vomiting, diarrhoea, anorexia • CNS disorders: seizure, tremors • Hypersensitivity: Similar to other βLs	• Antagonism with bacteriostatic drugs like CAP • ↓antibacterial activity when used concomitant with other βLs
13.	**Polypeptide Antibiotics**	
	• Minimal adverse effects through oral (GI disturbances) or topical administration <u>Parenteral administration :</u> • Nephrotoxicity: albuminuria, cylinduria, haematuria • Neurotoxicity (Neuromuscular paralysis) • Hypersensitivity (Mast cell degranulation) • Pain & irritation at site of IM injection	• Other nephrotoxic drugs can ↑plasma concentrations & toxicity. • Antagonism may occur with the penicillins & CAP • Colistin ↑ NM blocking effect of muscle relaxants
14.	**Glycopeptide Antibiotics**	
	• Toxicity information is only available for humans • Produce high systemic toxicity • Dose & time dependant ototoxicity & nephrotoxicity • Phlebitis, hypotension (IV injections) • Hypersensitivity • Pain & irritation at site of IM injection	• Exaggeration of nephrotoxicity or ototoxicity when used concomitant with other drugs causing the same viz. AGs • Anaesthetic drugs increase infusion reactions (hypotension, anaphylactoid reaction, pruritus & erythema)
15.	**Oxazolines**	
	• Relative safer, when used for shorter period • GI disturbances: anorexia, vomiting, diarrhoea • Superinfection: CDAD, pseudomembranous colitis <u>Long term use :</u>	• Aggravation of MAO inhibition with other MAO inhibitors • Co-administration with pethidine, dextromethorphan, TCAs, SSRIs &

	• Bone marrow suppression (thrombocytopenia) • Irreversible peripheral & optic neuropathy	meperidine may result in serotonin syndrome • Rifampin ↓ AUC of linezolid • Sympathomimetic agents, may cause ↑BP when combined with linezolid

GI= Gastro-intestinal, PG-fermenters= Post-gastric fermenters, βLs= Beta-lactam antibiotics, CNS= Central nervous system, CHF= Congestive heart failure, BA= Bioavailability, $t_{1/2}$= Half life, IM= Intramuscular, CAP= Chloramphenicol, NM= Neuromuscular, AGs= Aminoglycosides, QT= QT-segment of ECG curve, MRSA= Methicillin-resistant *Staphylococcus aureus*, FQs= Fluoroquinolones, LCSs= Lincosamides, UT= Urinary tract, BUN= Blood urea nitrogen, PABA= Para-aminobenzoic acid, CVS= Cardiovascular system, IV= Intravenous, PCT= Proximal convoluted tubule of renal nephron, TCs= Tetracyclines, MLs= Macrolide antibiotics, MAO= Mono-amino oxidase, CYP= Cytochrome P450, CDAD= *Clostridium difficile*-associated diarrhoea, TCAs= Tricyclic antidepressant, SSRIs= Selective serotonin reuptake inhibitors, AUC= Area under curve, ↑= Increase, ↓= Decrease.

V. Management and Prevention of ADRs in Veterinary Patients

It is necessary that the clinicians should be aware of the dangers associated with some of the drugs they deal with regularly[24]. Following are few recommendations and precautionary measure to prevent or minimize the antibacterial-associated adverse reactions [4,9,10,36].

- The first step in managing ADR is immediate discontinuation of culprit drug and its substitution with a relatively safe alternative preferentially from different class having unrelated chemical structures.
- If several medicines could be causative, the non-essential medicines should be withdrawn first, preferably one at a time, depending on the severity of the reaction.
- If the reaction is likely to be dose-related, it is better to reduce the dose rather unnecessarily withholding a drug.
- Medicines should be used only if necessary and when used, safest drug among the available alternatives should be chosen.
- Previous history of drug allergy should be kept into the consideration before prescribing the drugs, especially β-lactam antibiotics.
- Polypharmacy, fixed-dosed combinations and off-label drug used should be avoided.
- Clinical benefit-risk ratio should be assessed and accordingly treatment regimen should be planned.
- Doses and interval should be adjusted in patients with heart failure, liver and renal diseases.
- The drug-drug interactions should be considered when a patient is already on medication or when there is a need to prescribe multiple drugs concurrently.
- Client should be informed regarding possible ADRs so that they can notify to the clinicians and seek the medical help in emergency.
- Therapeutic monitoring of drugs should be carried out whenever necessary, especially with aminoglycosides.

VI. Conclusion

The drug-induced adverse reactions are usually encountered in veterinary as well as in medical practice. This review revealed that several commonly used antibacterial agents exhibit ADRs which is a major concern for clinicians. Among these, the antibacterials like chloramphenicol, sulphonamides and aminoglycosides possess high risk of developing adverse effects. Therefore, these drugs should be kept as reserve and should be used only when other safe alternative are not effective or benefit outweigh the risks, with proper care monitoring. On contrary penicillins, cephalosporins and macrolide antibiotics are seems to relatively safe. Antibacterial-associated ADRs range from minor reactions like mild digestive disturbances, tissue irritation, pain at the site of injection, ptyalism, malaise etc. to the more severe effects viz. neurotoxicity, renal failure, hepatotoxicity, cardiac dysrhythmia, fatal anaphylaxis, etc., which are life-threatening and eventually become lethal. Probability of occurrence and risk of the untoward reactions is higher in certain conditions such as renal and hepatic impairment; hypersensitivity; immune disorders species or breed predilection and individual susceptibility; pregnancy; young or old age; drug interactions and some other factors. The veterinary practitioner should be familiar with these adverse reactions further, the drug interactions should also be considered prior to use a drug so that harmful effect can be minimized.

References

[1] Dugassa J. Review on antibiotic resistance and its mechanism of development. 2017; 1(3):1–17.

[2] Sachi S, Ferdous J, Sikder MH, Azizul Karim Hussani SM. Antibiotic residues in milk: Past, present, and future. J Adv Vet Anim Res. 2019; 6(3): 315–332.

[3] Maddison JE, Watson ADJ and Elliott J. Antibacterial drugs. In: Maddison EJ, Page SW and Church DB,. Small Animal Clinical Pharmacology. Edn 2. Elsevier Limited, Philadelphia; 2008. pp. 147–85.

[4] Arunvikram K, Mohanty I, Sardar KK, Palai S, Sahoo G, Patra RC. Adverse drug reaction and toxicity caused by commonly used antimicrobials in canine practice. 2014; 7(6): 299-305.

[5] Abdou AK, Khadiga IA, El-Sharkawy RS. Adverse Drug Reaction and Nephrotoxicity Caused By Commonly Used Antibiotics in Dogs. 2016; 3(2): 290–6.

[6] Bennett PN and Brown MJ. Clinical Pharmacology. Edn 10. Elsevier Limited; 2008.

[7] Nasri H and Shirzad H. Toxicity and safety of medicinal plants. Journal of HerbMed Pharmacology 2013; 2(2): 21–2.

[8] Siroka Z, Svobodova Z. The toxicity and adverse effects of selected drugs in animals – overview. 2013; 16(1): 181–91.

[9] Sandhu HS. Essentials of Veterinary Pharmacology and Therapeutics. Edn. 2nd. Kalyani Publishers Ludhiyana; 2013.

[10] Edwards IR, Aronson JK. Adverse drug reactions : definitions, diagnosis and management. 2000; 356: 1255–9.

[11] Ebadi M. Desk Reference of Clinical Pharmacology. Edn 2nd. Boca Raton: CRC Press; 2008: 21-22.

[12] Maddison JE and Page SW. Adverse drug reactions. In: Maddison EJ, Page SW and Church DB. Small Animal Clinical Pharmacology. Edn 2. Elsevier Limited, Philadelphia; 2008. pp. 1–57.

[13] World Health Organization, 1972.
[Available at: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf]

[14] McQueen EG. Pharmacological basis of adverse drug reactions. In: Avery GS, Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics. Edn 2. ADIS Press, New York; 1980.

[15] Boothe DM. Adverse Drug Reactions in the Dog and Cat. World Small Animal Veterinary Association World Congress Proceedings, 2014.
[Available at: https://www.vin.com/apputil/content/defaultadv1.aspx?pId=12886&catId=64736&id=7054656]

[16] Ritter JM, Lewis LD, Mant TGK and Ferro A. A Textbook of Clinical Pharmacology and Therapeutics. Edn 5. Hodder Arnold, Great Britain; 2008: 45-77.

[17] Alam MS, Pillai KK, Aliul S, Abdi H, Kapur P, Pillai PK, et al. Adverse drug reaction monitoring during antimicrobial therapy for septicemia patients at a university hospital in New Delhi. The Korean Journal of Internal Medicine 2018; 33(6): 1203–1209.

[18] Bojrnsson ES. Hepatotoxicity by drugs: The most common implicated agents. International Journal of Molecular Sciences. 2016; 17(224): 1-7.

[19] Hoofnagle JH, Bjornsson ES. Drug-induced liver injury- Types and phenotypes. The new England Journal of Medicine 2019; 381(3): 264–273.

[20] Wiebe VJ. Drug Therapy for Infectious Diseases of the Dog and Cat. Edn 1. John Wiley & Sons, Inc., Iowa; 2015.

[21] Beco L, Guaguere E, Lorente MC, Noli C, Nuttall T, Vroom M. Suggested guidelines for using systemic antimicrobials in bacterial skin infections (2): Antimicrobial choice, treatment regimens and compliance. Vet Rec. 2013; 172(6): 156–160.

[22] Plumb DC. Plumb's Veterinary Drug Handbook. Edn 7. PharmaVet Inc., Stockholm; 2011.

[23] Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, Mclaughlin M. A Review of Antibiotic Use in Pregnancy. 2015; 35(11):1052–1062.

[24] Riviere JE and Papich MG. Veterinary Pharmacology and Therapeutics. Edn 10. JohnWiley & Sons, Inc., Hoboken; 2018.

[25] Brunton LL, Hilal-Dandan R and Knollmann BC. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. Edn 13. McGraw-Hill Education; 2018.

[26] VaniPrasad V and Koley KM. Synopsis of Veterinary Pharmacology and Toxicology. Edn 1. Vahini Publications, Parbhani; 2006.

[27] Griffin JP and D'Arcy PF. A manual of adverse drug interactions. Edn 5. Elsevier Science BV, Amsterdam; 1997.

[28] Magdesian KG. Antimicrobial Pharmacology for the Neonatal Foal. Vet Clin Equine 2017; 33: 47–65.

[29] Porsani M. Drug Reaction Caused by Clavulanate Amoxicillin in Dogs: Report of two Cases. MOJ Toxicol. 2017; 3(5):119–121.

[30] Randjelovic P, Veljkovic S, Stojiljkovic N, Sokolovic D, Ilic I. Gentamicin nephrotoxicity in animals: Current knowledge and future perspectives. EXCLI J. 2017; 16:388–399.

[31] Gelatt KN, Van Der WA, Ketring KL, Andrew SE, Brooks DE, Biros DJ, et al. Enrofloxacin-associated retinal degeneration in cats. 2001; 99–106.

[32] Vivrette SL, Acvim D, Bostian A, Bermingham E, Papich MG, Acvcp D. Quinolone-Induced Arthropathy in Neonatal Foals. Proceedings of the Annual Convention of the AAEP 2001; 47: 376–377.

[33] Trepanier LA. Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. Journal of Vetrinary Pharmacology and Therapeutics 2004; 27(3): 129-138.

[34] di Cerbo A, Pezzuto F, Guidetti G, Canello S, Corsi L. Tetracyclines: Insights and Updates of their Use in Human and Animal Pathology and their Potential Toxicity. The Open Biochemistry Journal 2019; 13(1): 1–12.

[35] Klebaniuk R, Tomaszewska E, Dobrowolski P, Kwiecien M, Burmanczuk A, Yanovych D, et al. Chloramphenicol-Induced Alterations in the Liver and Small Intestine Epithelium in Pigs. Annals of Animal Science 2018; 18(2):429–440.

[36] Davis JL. Recognizing and treating adverse drug reactions, 2011.
[Available at: https://www.dvm360.com/view/recognizing-and-treating-adverse-drug-reactions-proceedings-0