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Pharmacokinetics of Antimicrobials in Food Producing Animals

S. K. Bhavsar and A. M. Thaker

*Department of Pharmacology and Toxicology,
College of Veterinary Science and Animal Husbandry,
Anand Agricultural University, Anand, Gujarat,
India*

1. Introduction

Pharmacokinetics deals with study of absorption, distribution, metabolism and excretion (ADME) of drugs. Pharmacokinetics, the study of time course of drug concentrations in the body, provides means of quantifying ADME parameters. In a clinical situation pharmacokinetics provides the practitioners a useful tool to design optimally beneficial drug dosage regimen for patient. Understanding pharmacokinetic principles allows clinician to make more rational therapeutic decisions. It also provides conceptual understanding to utilize withdrawal time to prevent drug residues that remain in the milk and edible tissues of food producing animals.

Various steps involved in governing fate of drugs must be defined and quantified concentration of free, non-protein bound drug dissolved in serum or plasma is taken as reference point for pharmacokinetic analysis. Serum or plasma drug concentrations generally retract extra cellular fluid drug concentrations. A drug generally be present at its site of action in a tissue at sufficient concentration for a specific period to produce pharmacologic effect. This understanding is important in veterinary medicine where specific difference in any of ADME process significantly affect the extent and/or time course of drug absorption and disposition in the body.

The concentration of antimicrobial achieved at site of infection depends on systemic availability of the drug, which varies with the dosage form and route of administration. The chemical nature and physicochemical properties of the drug influence the extent of absorption, pattern of distribution and rate of elimination. Effective antimicrobial therapy depends on triad of bacterial susceptibility, pharmacokinetic characteristics of the drug and the dosage regimen.

Antimicrobials are administered either as flock medication in poultry and individually or group in swine and cattle. Systemic antimicrobial treatment is given orally through medicated feed or water, or by injections. Antimicrobials used in animals are generally the same to antimicrobials used in humans. Tetracyclines constitute the antimicrobials class quantitatively most used in animals followed by macrolides, lincosamides, penicillins,

sulfonamides, aminoglycosides, fluoroquinolones, cephalosporins and phenicols. The most common antimicrobial drug used as growth promoters include macrolides (tylosin and spiramycin), polypeptides (bacitracin), glycolipids (bambermycin), streptogramins (virginiamycin), glycopeptides (avoparcin), quinoxalines (carbadox and olaquinox) and ionophores (monensin and salinomycin).

In human and veterinary practice the primary concern in antimicrobial drug selection and use is the therapeutic outcome. Larger than therapeutic doses may lead to potential toxicity. Clinicians involved in the treatment of diseases in food animals have additional concern of the persistence of drug residue in the edible tissues after the disease has been treated. Adulteration of food supply with antimicrobial agents and other chemicals is growing concern to general public.

2. Beta-lactam antibiotics: Penicillins, cephalosporins and related drugs

Beta-lactam constitutes one of the most important and frequently used antimicrobial agents. The penicillins, cephalosporins, carbapenems, monobactams and β -lactamase inhibitors are referred to as beta-lactams antibiotics.

2.1 Penicillins

The Penicillins are a large group of naturally occurring and semi-synthetic antibiotics. The penicillins are organic acids available as sodium or potassium salts. The Penicillins (Pk_a 2.7) are predominantly ionized in plasma. Penicillins in general have relatively small apparent volumes of distribution (0.2-0.3 L/kg) and short half-lives (0.5-1.2 hours) in all species of domestic animals.

Penicillins are hydrolyzed & inactivated in the acidic pH of the stomach and therefore not absorbed orally except penicillin-V, aminopenicillins (ampicillin & amoxicillin) and isoxazolylpenicillins (cloxacillin, dicloxacilin & oxacillin). Aminopenicillins are absorbed poorly in horses and ruminants. Following oral administration, absorption of ampicillin in adult horses is only 2-3.5% (Sarasola & Mc Kellar, 1994; Ensink, et al, 1996). Systemic availability of oral amoxicillin is higher (2-10%) than ampicillin in adult horses. (Ensinic, et al, 1996; Wilson, et al, 1998). Serum concentrations of penicillins generally peak within 2 hrs of PO administration. Penicillins in aqueous solution are rapidly absorbed from parenteral administration. Penicillins suspended in vegetable oil vehicles or sparingly soluble penicillins (procaine penicillin G and benzathine penicillin G) administered parenterally absorbs slowly resulting in longer persistence of plasma and tissue drug concentrations.

Penicillins are widely distributed in body fluids & tissues. Protein binding of penicillins is low to moderate ranging from 30-60%. The penicillins have moderate volume of distribution and gets diffuse into extracellular fluid easily. Sufficient concentrations are achieved for susceptible bacteria in kidneys, synovial fluid, liver, lung, skin and soft tissues (Strover et al., 1981; Brown et al., 1982). Penicillins cross biologic membranes poorly. Entry of penicillin across blood-brain, placental, mammary or prostatic barriers is enhanced by inflammation or massive dose.

Penicillins are generally excreted unchanged except penicillin G, penicillin V, nafcillin, ticarcillin and aminopenicillins, which are metabolized to some extent by hydrolysis of β -lactam ring. The metabolites are inactive. Penicillins are eliminated entirely by Kidney (Glomerular filtration and tubular secretion), which results in very high level in the urine except nafcillin, which is excreted mainly in bile. Active tubular secretion of penicillins can be comparatively inhibited by organic acids such as probenecid. Penicillins are also eliminated in milk in trace amounts and may persist for 90 hours. Penicillin residue in milk has been detected after intrauterine infusion also.

2.2 Cephalosporins

The pharmacokinetic characteristics of cephalosporins are typical of penicillins. Very few cephalosporins (cephalexin, cephalexin, cephalexin, cephalexin & cefachlor) are acid stable and given orally. Pro-drug formations of such drugs enhance oral bioavailability. Cefadroxil is absorbed better in the foal than adult horses (Dufee et al., 1989). Most of the other cephalosporins are either administered IV or IM. Peak plasma concentration usually observes at ~ 30 min after parenteral administration.

Cephalosporins are widely distributed through most body fluids & tissues including kidneys, lung, joints, bone & soft tissues except prostate & CNS. The volume of distribution is <0.3 L/kg. Protein binding for most cephalosporins is low in animals compare to human. For example ceftriaxone & cefazolin has high (85-95%) protein binding in human as compared to dogs (19-25%) (Popick et al., 1987).

Cephalosporins are minimally metabolized in the liver. Several Cephalosporins like cephalothin, cephalixin, cephacetrile & cefotaxime are deacetylated to less active derivatives except ceftiofur, which is transformed to desfuroyl ceftiofur, which is largely responsible for its antibacterial efficacy. Most of the cephalosporins are excreted by renal tubular secretion except cefoperazone, which is largely excreted in the bile. In general cephalosporins have half-lives of 1 to 2 hours except some third generation cephalosporins like ceftiofur having half-life of 3-6 hr in cattle, 4 hours in dogs and 2.5 hr in horses. The pharmacokinetic parameters of some cephalosporins given to food animals like cattle, sheep and goat are given in Table 1.

2.3 Other Beta-lactam antibiotics

2.3.1 Carbapenems

Carbapenems differ from penicillins by the substitution of a CH_2 group for the sulphur in the five- membered ring attached to β -lactam ring. They have very broad spectrum of activity and are resistant to most β - lactamases. It includes imipenem, doripenem, ertapenem, meropenem and biopenem. The carbapenems are not absorbed orally, hence must be given parenterally. Following IV Injection, they are widely distributed to extra cellular fluid throughout body & achieve therapeutic concentrations in most tissues. Carbapenems have low volume of distribution like penicillins & cephalosporins. Following IM administration imipenem has excellent bioavailability (>95%) and distributed widely throughout body except CSF. Imipenem gets largely eliminated through kidneys and gets

metabolized in renal tubules by a dihydropeptidase enzyme. Cilastatin, an inhibitor of renal dipeptidase decrease renal metabolism of impenem, leading to increase in elimination half-life and decrease excretion of the drug largely in urine in active form. Half-life of carbapenem in patients having normal renal function is about 1 hour.

Cephalosporin	Animal species	Route	Dose (mg/kg)	C _{max} (µg/ml)	Vd (L/kg)	T _{1/2} (hr)	AUC (0-∞) (µg x h/ml)	Cl (ml/min/kg)	F (%)	Reference
Cephapirin	Cows (lactating)							12.7		Prades et al., 1988
Cephalexin	Calves				0.32	2.0		1.9		Garg et al., 1992
Cefazolin	Calves				0.17	0.62		5.8		Soback et al., 1987
Ceftriaxone	Goat	IV	20	-	0.58	1.50	77.51	4.50	-	Tiwari et al., 2009
		IM	20	21.51	0.53	2.03	66.78	3.04	59	
	Sheep	IV	10	-	0.41	1.21	42.65	3.91	-	Swati et al., 2010
		IM	10	15.53	0.43	2.24	47.68	2.22	64	
	Calves (Buffalo)	IV	10	-	0.48	1.27	40.0	4.40	-	Gohil et al., 2009
			10	15.8	1.53	4.38	29.67	4.01	70.2	
		IM	10	-	0.44	1.58	57.35	3.15	-	Maradiya et al., 2010
			10	15.34	1.16	5.02	28.15	2.71	47	
Cefepime	Goat	IV	10	-	0.52	2.71	78.38	2.19	-	Patni et al., 2008
		IM	10	15.75	-	4.89	93.12	1.27	69	
	Sheep	IV	20	-	0.42	2.54	135.5	2.48	-	Patel et al., 2010
		IM	20	26.34	1.11	5.17	140.90	0.15	103	
	Calves (Cow)	IV	5	-	0.57	3.70	47.73	1.81	-	Patel et al., 2006a
		IM	5	8.61	0.99	6.71	47.45	1.72	98	
Cefoxitin	Calves					1.12				Soback, 1988
Ceftazidime	Sheep				0.36	1.60				Rule et al., 1991
Cefoperazone	Calves					0.89				Carli et al., 1986
	Sheep	IV	47		0.16			2.7		Guerrini et al., 1985
Moxalactam						2.40				Soback, 1989

Table 1. Pharmacokinetic parameters of selected cephalosporins administrated to food producing animals.

2.3.2 Monobactams

Monobactams are simple monocyclic β-lactam compounds active only against bacteria or anaerobes. Aztreonam is a synthetic monobactam. It is not absorbed orally. It is administered IV or IM having extensive distribution throughout body including CSF. It is having elimination half-life of 1.6 hour in man.

2.3.3 β -lactamase inhibitors

Beta lactamase enzyme production is a major factor in constitutive or acquired resistance of bacteria to β -lactam antibiotics. These drugs are combined with penicillins & cephalosporins to prevent degradation. It includes clavulanic acid, sulbactam and tazobactam.

Clavulanic acid is a synthetic compound. It is combined with amoxicillin (4:1) or ticarcillin (15:1). Clavulanic acid is well absorbed following oral administration having bioavailability more than 60%. It has widespread tissue distribution in extra cellular fluid but penetration in milk and CSF is poor. It gets largely eliminated unchanged in urine. Sulbactam (penicillinic acid sulfonate) is synthetic derivative of 6-aminopenicillinic acid. It is combined with either ampicillin or cefoperazone. The combination of sulbactam ampicillin gets absorbed after IM injections, distributes well into tissues and penetrates CSF through inflamed meninges. It is poorly absorbed orally but a pro-drug "sultamicillin" having double esters linkage of sulbactam with ampicillin gets absorbed from small intestine. Tazobactam is combined with piperacillin (piperacillin: tazobactam, 8:1) having pharmacokinetic properties similar to β -lactam drugs.

3. Tetracyclines

Tetracyclines are a group of broad- spectrum antibiotics having a nucleus of four cyclic rings. The tetracyclines are crystalline amphoteric substances that can exist as acid or base salts. The tetracyclines are strong chelating agents. Its chelation with calcium causes tooth discoloration. Tetracyclines include chlortetracycline, oxytetracycline, tetracycline, doxycycline and minocycline.

Tetracyclines have low absorption following oral administration except doxycycline. The tetracyclines are relatively lipophilic drugs that remains ionized in the gastrointestinal tract. Oral absorption of tetracyclines gets drastically reduced in the presence of food (Neilsen and Gurd-Hansen 1996). Its oral absorption decrease with co-administration of food, dairy products, polyvalent cations (Ca^{++} , Mg^{++} , Fe^{++} , Al^{+++}), Kaolin/pectin preparations, ion containing supplements and antacids. Tetracyclines (oxytetracycline) can be administrated IV or IM. All tetracycline produce varying degree of tissue irritation on parenteral administration. The bioavailability of orally administrated oxytetracycline is 5% compared to 37% for chlortetracycline in non fasting calves. The long acting formulation of oxytetracycline used for IM administration to food animals have long acting effect due high dosage and prolonged persistence at the site of IM injection as a result of tissue irritation (Nouws et al.,1990). The bioavailability of most tetracyclines is very poor following oral administration in pigs. Intravenous administration of oxytetracycline is preferred over IM injection in horses as it results in higher and more persistent serum concentration.

Tetracyclines bind to plasma proteins at varying degrees in different species of animals. Tetracyclines are widely distributed in most tissues including kidney, liver, lungs, bile and bones. Tetracyclines have volume of distribution in excess of 1.0 L/kg indicating higher drug concentration intracellular or binding to tissues. Tetracyclines are more lipophilic than other classes of antibiotics hence it can cross lipid membrane easily. Minocycline and doxycycline attain high concentration in brain, ocular tissues, spinal fluid and prostate than other tetracyclines. Doxycycline has high affinity for intracellular accumulation than other tetracyclines (Davis et al., 2006). Tetracyclines cross the placenta and enter foetal circulation and are secreted in milk of lactating animals.

With exception of lipid soluble tetracyclines (doxycycline, minocycline), the tetracycline antibiotics are not metabolized to a significant extent in the body. About 60% of the dose gets eliminated in urine via glomerular filtration and 40% in faeces. Doxycycline gets excreted largely in the large intestine. Doxycycline & minocycline undergo entero-hepatic circulation, which contributes to their longer half-life (6-10 hr) than tetracycline that are eliminated mainly by renal excretion.

4. Aminoglycosides

The aminoglycosides are bactericidal natural and semi-synthetic antibacterials primarily used for treatment of gram negative infections and staphylococci. The group consists of hexose nucleus to which amino sugars are attached by glycosidic linkages. The aminoglycosides are basic polycations with pKa value ranging from 7.2 to 8.8. The chemical structure determines the antimicrobial activity, resistance patterns and inherent propensity to cause toxicosis. The group includes drugs like gentamicin, amikacin, kanamycin, apramycin, tobramycin, neomycin, streptomycin, dihydrostreptomycin, paromomycin and spectinomycin.

The pharmacokinetics of the aminoglycosides is similar across most veterinary species. However, variability within each animal population is large that necessitates close monitoring of serum concentrations to optimize efficacy and minimize toxicosis. Equines receiving multiple doses of parenteral amino-glycosides require therapeutic drug monitoring (Martin & Riviere, 1998)

Aminoglycosides are poorly absorbed (<10%) from gastrointestinal tract because of their highly polar and cationic nature. Aminoglycosides given orally to young animals (neonate) with enteritis, significant absorption occur leading to violative tissue residues. The aminoglycosides are well absorbed following IM or SC injection. The peak serum concentration is achieved within 30 to 45 minutes following extravascular administration. Intravenous and intraperitoneal routes produce rapid effects but should be avoided because of serious side effects. Following intrauterine or intramammary infusion to cows, gentamicin is well absorbed and results in prolonged tissue residues. Absorption is extremely rapid and complete, if aminoglycosides are instilled into body cavities that contain serosal surfaces.

Aminoglycosides are extensively distributed in extracellular fluid, as these are large molecules and highly ionized at physiological pH. They are poorly lipid soluble and have limited capacity to enter cells and penetrate cellular barriers. These drugs attain very low concentration in cerebrospinal, respiratory and ocular fluid. In the renal tubular cells and the endolymph and perilymph of inner ear, aminoglycoside attain high concentration causing nephro and oto-toxicity, respectively. Their apparent volume of distribution is relatively small (<0.35L/Kg). The amino glycosides binds poorly (<20%) to plasma proteins. Gentamicin is distributed into synovial fluid in normal horses; local inflammation may increase drug concentration in the joint.

The aminoglycosides are not metabolized and are excreted largely as such (~90%) in urine by glomerular filtration. Plasma elimination half lives are short (1-2 hr) in domestic animals

having normal renal function. It increases to 24-48 hr in patients having renal insufficiency. The disposition of aminoglycosides varies among animals because of differences in glomerular filtration rates. The prolonged terminal elimination phase of aminoglycosides has major implications for veterinary therapeutics in food producing animals. Aminoglycosides accumulate in renal cortex for prolonged periods of time, resulting in tissue residues even after short periods of administration.

5. Fluoroquinolones

Fluoroquinolones are synthetic antibacterial agents introduced in veterinary medicine in the 1980s. Currently available quinolones contain basic structure of 4-quinolone (Short for 4-oxo-1,4- hydroquinoline) with carboxylic acid moiety. Fluoroquinolones are amphoteric molecules having pKa ranging from 6.0-6.5 (Carboxy group) and 7.5-8 (nitrogen of piperazine group). Fluoroquinolones at physiological pH occurs as zwitterions. Fluoroquinolones commonly used in veterinary medicine include enrofloxacin, difloxacin, orbifloxacin, marbofloxacin, ibafloxacin and danofloxacin. Other compounds having potential interest in veterinary practice include ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin and pradofloxacin.

The fluoroquinolones have good rate and extent of absorption after oral administration in monogastric animals and pre-ruminant calves. Presence of food has little effect on oral absorption. In dogs, cats and pigs, oral absorption of fluoroquinolones approaches to 100%, but in large animals it is less. Enrofloxacin is more lipid soluble than ciprofloxacin and has a higher oral bioavailability than ciprofloxacin in horses and small animals. The oral bioavailability of enrofloxacin is 63% (Giguere et al., 1996) in adult horses and 42% in foals (Birmingham et al., 2000). Absorption is complete following IM and SC Injection of fluoroquinolones. The pharmacokinetic parameters of some fluoroquinolones given to food animals like cattle, sheep, goat, pig and chicken are given in Table 2.

Following absorption, fluoroquinolones show rapid and extensive tissue distribution due to hydrophilic nature and low (<50%) protein binding. In general, fluoroquinolones concentration in interstitial fluid, skin and bones are 35-100% of those obtained in serum, where as bronchial secretions and prostatic concentrations are two to three times of corresponding serum concentrations. Penetration into CSF is approximately 25% of serum concentration (Davis et al., 2002). Fluoroquinolones attain high intracellular concentrations in macrophages and neutrophils. Intracellular concentrations are 4 - 10 times greater than plasma concentrations.

The fluoroquinolones are largely eliminated uncharged in the urine by glomerular filtration and active tubular secretion, except difloxacin, which is excreted largely (80%) in faeces. Parent compound as well as metabolites of some fluoroquinolones is excreted in bile and urine. Enrofloxacin undergoes de-ethylation to active metabolite ciprofloxacin. In cattle the proportion of ciprofloxacin in plasma was 25 - 41% following administration of enrofloxacin (Davis et al., 2002). The ciprofloxacin concentration residues were present in tissue of chicken 12 days after dosing of enrofloxacin (Anadon et al., 1995). Pefloxacin gets completely metabolized to active metabolite norfloxacin. The elimination half-life (3-6 hr) of fluoroquinolones is dependent on the drug and animal species.

Fluoro quinolone	Animal species	Route	Dose (mg/kg)	C _{max} (µg/ml)	Vd (L/kg)	T _{1/2β} (hr)	AUC (0-∞) (µg x h/ml)	F (%)	Reference	
Ciprofloxacin	Sheep	IV	5	-	1.67	1.88	8.40	-	Patel et al., 2004	
		IM	5	0.95	3.40	3.67	5.48	68		
	Calves (cow)	IV	5	-	1.67	1.80	7.90	-	Bhavsar et al., 2004	
	Calves (Buffalo)	IV	5	-	1.98	1.25	4.56	-	Sarvaiya et al., 2006	
	Pigs	IV	3.06	0.17	3.83	2.57	2.88	37	Nouws et al., 1988	
Chicken	PO	5	4.67	2.0	9.0	78.04	70.0	Atta and Sharif, 1997		
Levofloxacin	Poultry (Broiler)	IV	10	-	3.25 (Vdss)	3.18	11.33	-	Varia et al., 2009	
		PO	10	0.93	-	3.64	6.70	59.5		
Enrofloxacin	Cattle	SC	12.5	0.96	-	6.79	14.95	-	Davis et al., 2006	
		IV	8	0.81	-	7.28	7.51	-	Ter Hune et al., 2005	
		IV	5	-	1.63	1.68	7.42	-	Kartinen et al., 1997	
		IM	5	0.73	-	5.9	82			
		SC	5	0.98	-	5.55	137			
			2.5	-	2.98	2.82	5.28	-	Bergante et al., 1999	
	Goat	IV	5	6.7	1.3	1.1	6.7	-	Rao et al., 2002	
	Sheep	-		5	2.69	1.15	4.8	57.5	98.07	Birmingham and Papich, 2002
			IM	2.5	-	2.18	3.73	5.47	85.0	Mengozi et al., 1996
			PO	2.5	0.78	1.3	3.8	10.4	60.6	Pozzin et al., 1997
		Pig	IM	2.5	0.61	3.5	7.73	9.94	95	Richez et al., 1997
				2.5	0.75	3.95	5.5	5.03	101	Pijpers et al., 1997
		Chicken	IV	10.0	1.88 (PO)	5.0 (IV)	5.6	16.17	89.2	Knoll et al., 1999
	PO		10.0	1.5	-	14	35	-	Da Silva et al., 2006	
Danofloxacin	Cattle	IV	6	1.7	-	4.21	9.72	-	Ter Hune et al., 2005	
		IM	1.25	0.28	2.04	2.25	132.85	289	Shem-Tov et al., 1998	
		IM	5	0.82	-	2.9	4.7	78	Mann and Frame, 1992	
	Goat	SC	1.25	0.33	3.8	4.67	2.29	110	Aliabdi and lees, 2001	
	pig	IM	5	0.8	-	8.0	6.0	76	Mann and Frame, 1992	
Marbofloxacin	Goat	IM	2	1.9	1.3 (Vdss)	7.2	8.44	100.7	Waxman et al., 2001	

Table 2. Pharmacokinetic parameters of selected fluoroquinolones administrated to food producing animals.

6. Sulphonamides and potentiated sulphonamides

The sulphonamides are oldest antimicrobial compounds, derivatives of sulphanilamide which was obtained from the azo dye "prontosil". Sulphonamides are white crystalline powders that are quite insoluble. They are more soluble at an alkaline pH than an acidic pH. Solubility of sulphonamides increases in the presence of another sulphonamide in the solution because it follows law of independent solubility. The sodium salts of sulphonamides are readily soluble in water. These solutions are highly alkaline (used for parenteral preparation) in reaction except sodium sulphonamide which is near neutral and used for ophthalmic instillation. The pKa values of sulphonamides range from 10.4 (sulfanilamide) to 5.0 (sulfisoxazole). They exist in lipid soluble non-ionised form in biologic fluids of pH lower than their pKa. Sulphonamides commonly used in veterinary medicine include sulphadimethoxine, sulphamethazine (sulphadimidine), sulphaquinoxaline, sulphamerazine, sulphathiazole, sulphasalazine, sulphadiazine, Sulphabromomethazine, sulphaethoxy pyridazine, sulphisoxazole and sulphachlorpyridazine. The potentiated sulphonamides are combination of a sulphonamide with diaminopyrimidine compounds (trimethoprim or ormetoprim). Potentiated sulphonamide combinations used in veterinary practice includes Trimethoprim - sulphadiazine, Trimethoprim - sulphamethaxazole, Trimethoprim - sulphachlorpyridazine and ormetoprim - sulphadimethoxine.

Most sulphonamides (except gut acting and topical sulphonamides) get well absorbed following oral administration. The absorption rate is affected by the solubility of sulphonamides and presence of ingesta in the gastrointestinal tract. In general dogs, cats and birds absorb sulphonamides rapidly, pigs take some time and ruminants require much longer time. In ruminants, age and diet markedly affect oral trimethoprim and sulphadiazine disposition in calves. Orally administered sulphadiazine (30mg/kg) was absorbed slowly in calves fed milk diets, with absorption slightly higher in ruminating calves. Trimethoprim was absorbed in pre-ruminant calves but not absorbed in mature ruminants after oral administration (Shoaf et al., 1987).

Sulphonamides are widely distributed throughout body including soft tissues, CNS (cerebrospinal fluid) and joints (synovial fluid). Plasma protein binding varies from 15 -90 % depending on sulphonamide to sulphonamide and species to species. Extensive (>80%) protein binding increases half-life. Sulfonamides are weak acids and trimethoprim is a weak base. Trimethoprim has higher volume of distribution than sulfonamide due to ion trapping of trimethoprim in tissues. Calculation of dosages of sulphonamides to maintain steady state of 100 µg/ml requires consideration of the extent of protein binding, apparent volume of distribution and half-life as it varies between individual within a species.

Sulphonamides and trimethoprim are metabolized faster and more extensively by herbivores than carnivore or omnivores. Acetylation of NH₂ group on N-4 is a major mechanism of metabolism. Hydroxylation of methyl group on the pyrimidine ring and carboxylation also occurs. Ruminants metabolize sulphonamides by acetylation pathways and acetylated metabolites are the major urinary metabolites in cattle, sheep and swine. Acetylated metabolites are less soluble than the parent compound and increase risks of renal tubular injury due to precipitation and crystal formation. The canines' lack the ability to acetylate sulphonamides, relying on alternate metabolic pathway. Glucuronide conjugation and aromatic hydroxylation are two additional pathways for sulphonamide metabolism. Sulphonamide metabolites are therapeutically inactive (N 4- acetyl metabolites) or have reduced therapeutic activity (hydroxy metabolites).

Sulfonamides are excreted in urine. Renal excretion mechanisms include glomerular filtration of free drug in the plasma, active carrier-mediated proximal tubular excretion of ionized unchanged drug and metabolites and passive reabsorption of nonionized drug from distal tubular fluid. Urinary alkalization increases both the fraction of dose that is eliminated by renal excretion and the solubility of sulphonamides in the urine.

7. Peptide antibiotics: Polymyxins, glycopeptides and bacitracin

7.1 Polymyxins

Polymyxins are group of N-mono-acetylated decapeptides. Polymyxin B and polymyxin E (colistin) are chemically related and therapeutically useful. The polymyxins are not absorbed into the body when given orally. Polymyxin B sulfate or colistin methane sulphonate sodium is given parenterally for systemic therapy. Following absorption polymyxins bind moderately (70-90%) to plasma proteins. Polymyxins bind extensively to muscle tissues. It binds to mammalian cell membrane and accumulates following long term dosing. They are slowly excreted unchanged by glomerular filtration in the urine. The polymyxins are highly nephrotoxic damaging the renal tubular epithelial cells.

7.2 Glycopeptides

Vancomycin, teicoplanin and avoparcin are glycopeptide antibiotics. The former two have been considered as the drugs of “last resort” to treat serious infections due to drug resistant gram-positive bacteria in human. Vancomycin and avoparcin are used in veterinary medicine in some countries.

Vancomycin is poorly absorbed following oral administration. Its tissue distribution is poor following parenteral administration. Most of the intravenously administered drug is excreted through the kidneys, with small proportion excreted in bile. Vancomycin hydrochloride is given IV as infusion and it requires monitoring in patients with renal impairment. Teicoplanin is not absorbed after oral administration. Absorption and distribution into tissue and extracellular fluid is excellent following IM Injection. It gets eliminated entirely in urine.

7.3 Bacitracin

It is polypeptide product derived from *Bacillus subtilis*. It is bactericidal to Gram-positive bacteria but has little activity on Gram-negative organisms. It is highly nephrotoxic after parenteral administration. It is only used for topical treatment of superficial infections of the skin and mucosal surfaces. In veterinary medicine it is used at low dose as growth promoter in chicken.

8. Lincosamides, pleuromutilins and streptogramins

8.1 Lincosamides

Lincosamides are a group of monoglycoside antibiotics containing amino-acid like side chain. It includes lincomycin, clindamycin and pirlimycin. Lincosamides are basic compounds with pKa of 7.6. They have high lipid solubility and large apparent volume of distribution.

Lincomycin is rapidly but incompletely absorbed following oral administration (20-50%) in pigs (Hornish *et al.*, 1987). Peak levels are achieved within 60 minutes following oral administration and 2-4 hr after IM Injection. It is well distributed in tissues (liver, kidney, muscle & skin) with low levels in CSF (Vd: 1-1.3 L/kg). Following oral administration most of the drug gets excreted through faeces (85%) and remainder in urine. Following IM Injection 38% gets excreted in faeces and 49% in urine.

Clindamycin is 7-chlorolincomycin having better antibacterial effect compared to lincomycin. Clindamycin absorbs better from gastrointestinal tract than lincomycin. It is distributed well to tissues and attains high intracellular concentration (Vd: 1.6-3.1 L/kg). It also achieves effective concentration in bone. Following parenteral administration half life ranges from 3.2 hr (IV) to 5-7 hr (IM or SC). It has excellent bioavailability (80-100%) following IM Injection.

8.2 Pleuromutilins

Tiamulin and valnemulin are semisynthetic derivatives of naturally occurring diterpene antibiotic pleuromutilin. Tiamulin hydrogen fumarate is used for oral administration whereas tiamulin base is used for Injection. Valnemulin hydrochloride is used as medicated feed premix. Tiamulin gets rapidly absorbed after oral administration in monogastric species but gets inactivated in rumen if given orally to ruminants. It has half life of 25 minutes following parental administration (Ziv *et al.*, 1983). It gets concentrated into milk as it is more lipophilic having pKa- 7.6. Valnemulin bioavailability exceeds 90% in pigs when given with feed.

8.3 Streptogramins

Streptogramins are a group of natural (virginiamycin, pristinamycin) or semisynthetic (quinupristin/dalfopristin) cyclic peptides. Virginiamycin is used in veterinary medicine as growth promoter (5-20 ppm). It is not absorbed after oral administration. Its use as growth promoter has been banned in several countries because of resistance in enterococcal isolates.

9. Macrolides, azalides and ketolides

The macrolide antibiotics are a group of structurally similar compounds containing 12-20 atoms of carbon in lactone ring. Various combinations of deoxy sugars are attached to lactone ring by glycosidic linkages. Macrolides used in veterinary medicine include erythromycin, tylosin, spiramycin, tilmicosin and tulathromycin. Other macrolides like oleandomycin and carbomycin have been used as feed additives for growth promotion in food animals.

9.1 Erythromycin

It is base having pKa of 8.8. It is poorly soluble in water and unstable in gastric acid. Erythromycin base is absorbed well following oral administration but it is highly susceptible to degradation from gastric acids. Erythromycin base in enteric-coated formulation or erythromycin estolate or stearate or phosphate or ethyl-succinate ester can be given orally. The stearate form is hydrolyzed in the intestine to the base and ethylsuccinate and estolate ester forms are hydrolyzed in the body to the active base. The presence of food in the

stomach interferes quite markedly with oral absorption. Aqueous solution of erythromycin glucophate and lactobionate forms can be given IV. Pain and irritation at site of Injection prohibits use of erythromycin by SC or IM routes. The drug is well distributed in the body, being concentrated in the tissue like lungs, liver, spleen, heart, kidney and bile, prostatic, seminal, pleural and peritoneal fluids. Prostatic fluid concentrations are approximately half that of serum concentration. Penetration of erythromycin to CSF is low. The drug is largely metabolized by demethylation and metabolites are excreted largely in bile, which is lost in faeces. Urinary excretion is only 3-5% of administered dose. The drug has half life of 3-4 hr in cattle.

9.2 Tylosin

Tylosin is more extensively used as a feed additive to promote growth in food-producing animals. Tylosin is a weak base (pKa 7.1) and is highly lipid soluble. The drug has good absorption from gastro-intestinal tract. It is widely distributed in tissues like lung, liver, spleen, heart and kidney. It is metabolized in liver and excreted via the bile and faeces. The elimination half-life in dogs and cattle is about 1 hr with apparent volume of distribution of 1.7 and 1.1 L/kg, respectively. The half-life is longer (4 h) in sheep, goat and pigs.

9.3 Tilmicosin

It is semisynthetic derivative of tylosin. It has slow absorption and low bioavailability (22%) in cows. It has large volume of distribution (>2 L/ kg), with accumulation and persistence in tissues like lung. The drug administered to cow (10 mg/kg, SC) resulted in milk concentration > 0.8 µg/ml for eight to nine days (Ziv et al.,1995)

9.4 Spiramycin

Spiramycin has quite exceptional ability to concentrate in tissues, resulting in tissue concentrations reaching 25-60 times those of serum. Persistence of drug residues for prolonged periods limits its use in food producing animals.

9.5 Tulathromycin

Tulathromycin is an azalide derivative of erythromycin. It is rapidly and extensively absorbed from SC & IM injection in cattle and pigs having bioavailability of 90%. The drug has half-life of 90 hr. The apparent volume of distribution following IV administration is 12 L/Kg. Lung concentrations are 25-80 times higher than serum concentrations.

9.6 Roxithromycin, dirithromycin, clarithromycin and azithromycin

The newer macrolides are acid stable, produce few gastro-intestinal side effects, have higher oral bioavailability and longer elimination half- lives and produce higher therapeutic tissue concentration as compared to erythromycin. Oral bioavailability of azithromycin is 97% in dogs and about 50% in cats and foals. Elimination half-life of azithromycin is 20 hr and 30 hr in foals and cats, respectively. Clarithromycin half-life (4.8 hr) is shorter than azithromycin but longer than erythromycin (1 hr) in foals. The major route of excretion is bile and intestinal tract for azithromycin. The major route of excretion for clarithromycin is kidney. Tissue concentration of azithromycin is 10-100 times of those achieved in serum. The

extensive tissue distribution of azithromycin is due to its concentration within macrophages and neutrophils.

9.7 Ketolides

Ketolides are members of a new semisynthetic 14 membered ring macrolide, with a 3-keto group instead of a α -L cladinose on the erythronolide A ring. It includes telithromycin and cethromycin, which are given orally. Their pharmacokinetics display a long half-life as well as extensive tissue distribution and uptake into respiratory tissues and fluids, allowing once daily dosing

10. Chloramphenicol and derivatives

10.1 Chloramphenicol

Chloramphenicol is a derivative of dichloroacetic acid and contains a nitrobenzene moiety. It is slightly soluble in water and freely soluble in propylene glycol and organic solvents. Chloramphenicol base or its palmitate salt is used for oral administration. Chloramphenicol palmitate is hydrolyzed in the small intestine by esterases, which release the free base form of chloramphenicol to systemic circulation. Chloramphenicol succinate is freely soluble in water and is used for IV or IM administration. It gets hydrolyzed in plasma to produce active drug. Pharmacokinetic parameters of chloramphenicol in food producing animal species are summarized in table 3.

Animal species	Route	Dose (mg/kg)	Formulation	Vd (L/kg)	T _{1/2β} (hr)	Reference
Cattle	IV	40	Base	0.35	2.81	Sanders et al., 1988
	IM	90	Base	-	1.35	
	SC	90	Base	-	1.15	
Calves	IV	25	Base in Propylene Glycol	1.03 (1 day old) 0.81 (7 day old) 0.90 (14 day old) 0.69 (28 day old) 1.38 (9 months old)	7.56 (1 day old) 5.96 (7 day old) 4.0 (14 day old) 3.69 (28 day old) 2.47 (9 months old)	Burrows et al., 1983
Sheep	IV	30	Base	0.69	1.70	Dagorn et al., 1990
	IM	30	Base	-	2.71	
	SC	30	Base	-	17.93	
Goats	IV	25	Succinate	1.68	1.22	Kume and Garg, 1986
	IV	25	Succinate	1.96	1.29	
	IM	25	Succinate	3.02	1.46	
	IM	25	Succinate	2.77	1.45	
	IV	10	Succinate	0.31	1.47	Abdullah and Baggot, 1986
Pigs (Adult)	IV	22	base	1.05	1.3	Davis et al., 1972
Piglets	IV	25	Base	0.94	12.7	Martin and Weise, 1988
Chicken	IV	20	Succinate	0.24	8.32	Atef et al., 1991
	IM	20	Succinate	0.44	7.84	
	PO	20	Succinate	0.41	8.26	

Table 3. Pharmacokinetic parameter of chloramphenicol in food producing animal

Chloramphenicol is well absorbed from gastro-intestinal tract in monogastric and pre-ruminant calves. The oral bioavailability in foals is 83%. Chloramphenicol palmitate is poorly absorbed in cats. Chloramphenicol administered orally to ruminants gets inactivated in rumen. High lipid solubility and low plasma protein-binding (30-46%) enable it to attain effective concentration most tissues and body fluids including cerebrospinal fluid and central nervous system. It also get readily diffuse into milk and pleural and ascetic fluids. It also readily crosses the placenta and achieves high concentration in fetus. The drug has large volume of distribution (1-2.5 L/kg) due to its lipophilic nature.

Chloramphenicol is metabolized in the liver. Phase-II glucuronidation is the principal pathway producing metabolite chloramphenicol glucuronide. Rapid metabolic clearance produces short half-lives in many species and requires frequent administration. The elimination half-life of chloramphenicol varies widely among species. It is short (1hr) in horses (Sisodia et al, 1975) and long (5-6 hr) in cats (Watson, 1991). Most of the absorbed chloramphenicol (80%) gets excreted into the urine as inactive metabolite via tubular secretion.

10.2 Thiamphenicol

Thiamphenicol is a semisynthetic structural analogue of chloramphenicol, in which the p-nitro group has been replaced by a sulfomethoxyl group. Absorption and distribution are similar to those of chloramphenicol. Bioavailability in pre-ruminant lambs and calves is 60 % following oral administration. It is well distributed in the body. Thiamphenicol is not eliminated by hepatic glucuronide conjugation but excreted unchanged in the urine. The pharmacokinetics of thiamphenicol follow allometric scaling, in that values of elimination half-life and volume of distribution increase with body size (Castells , 2001).

10.3 Florfenicol

Florfenicol is a fluorinated derivative of thiamphenicol, in which the hydroxyl group has been replaced with fluorine. The oral bioavailability of florfenicol is 89% in calves. Bioavailability following IM injection and intramammary infusion in lactating dairy cattle is 38% and 54%, respectively. Florfenicol is well distributed into many tissues and fluids including lungs, muscle, bile, kidney and urine. Concentrations in brain and CSF are $\frac{1}{4}$ to $\frac{1}{2}$, respectively of the corresponding concentrations in plasma. The drug has volume of distribution of 0.7-0.9 L/kg with low plasma protein binding (13-19%) in cattle. Most of the administered dose gets excreted as the parent drug (64%) in urine of cattle. Florfenicol amine metabolites persist longer in tissues of cattle and are used as marker residue for withdrawal determination. The elimination half-life is 2-4 hr in cattle. The commercially available formulation of florfenicol is long-acting, so that “flip-flop” kinetics occur, where elimination is prolonged due to slow absorption from the injection site.

11. Miscellaneous antimicrobials

11.1 Ionophore antibiotics

Carboxylic ionophore polyether antibiotics are *streptomyces* products used as growth promoters. Ionophore antibiotics used in veterinary medicine include monensin, lasalocid, maduramicin, narasin and salinomycin.

Following oral administration, monensin gets rapidly and completely absorbed in monogastric animals. In ruminants, oral bioavailability of monensin is 50%. Ionophore antibiotics do not attain higher concentration in tissues even at larger doses. Ionophores are rapidly and extensively metabolized in the liver and the metabolites are excreted in the bile and eliminated in the faeces. Horses are most sensitive to monensin toxicity because of very slow elimination as compared to cattle.

11.2 Nitrofurans

Nitrofurans are broad spectrum antimicrobials. They are used topically because of toxicity following systemic use. Nitrofurans are carcinogenic, hence their use in food animal has been banned in several countries (United States, Canada and European Union) of the world. In veterinary medicine, nitrofurazone is still used in non-food animals for skin infections.

11.3 Nitroimidazoles

The nitroimidazoles like metronidazole, dimetridazole, ronidazole, tinidazole and ipronidazole were once widely used in veterinary medicine but because of potential carcinogenicity, their use is banned in several countries (United States, Canada and European Union). Metronidazole is still used in companion animals against anaerobes & protozoa.

Metronidazole is absorbed rapidly in monogastric animals following oral administration. The drug has oral bioavailability of 75-85% in horses and 59-100% in dogs (Neff-Devis et al., 1981; Steinman et al., 2000). It is lipophilic and widely distributed in tissues. It penetrates bone, abscesses and the central nervous system. It crosses the placenta and also distributed to milk attaining concentration similar to those in plasma. The drug has volume of distribution of 0.7 to 1.7 L/kg in mares, 0.95 L/kg in dogs and 0.8 L/kg in cow calves. Metronidazole is primarily metabolized in the liver by oxidation and conjugation. Parent drug & metabolites are excreted in urine & faeces. The drug has half-life of 3-4 hr in horses, 8 hr in dogs and 1.9 hr in cow calves. Following oral administration in cow calves and sheep, half-lives were 4.38 & 1.72, respectively. Oral bioavailability in calves was 33.7 percent (Patel et al., 1993; Bhavsar & Malik, 1994).

11.4 Rifamycins

Rifampicin is the most important synthetically modified derivative of natural antibiotics rifamycins. Rifampicin is soluble in organic solvents and water at an acidic pH. The drug gets rapidly absorbed after oral administration in calves, dogs and horses. In horses, bioavailability is low and administration with food prolongs the time to maximum serum concentration. Rifampin is very lipophilic and penetrates most tissues including milk, bone, abscesses and central nervous system. It is well distributed in milk. It crosses placenta and is teratogenic in rodents. The volume of distribution of rifampin in horses is 0.6 - 0.9 L/kg. It is highly bound to plasma proteins. The biotransformation and elimination of rifampin in animals is not well known. The elimination half-life of rifampin in horses is 6-8 hrs after IV injection and 12-13 hrs after oral administration. In dogs, elimination half-life is 8 hrs. Rifampin causes induction of hepatic enzymes in many species.

12. Animal origin foods and antimicrobial drug residues

Food safety is one of the most significant issues for animal produce. During last several years great concern has been shown about the presence of chemical adulterants or residues especially antimicrobials and pesticides in the meat, poultry egg and milk. A chemical residue is either the parent compound or metabolite of that parent compound that may accumulate, deposit or otherwise be stored within the cells, tissues, organs or edible products of an animal following its use to prevent, control or treat animal disease or to enhance production. Residues can also result from unintentional administration of drugs or food additives. Contamination of the food supply with chemical residue is rarely an intentional act and usually results either from failure to observe the correct meat withdrawal or milk discard time for a drug after it has been used to treat a disease process in food animals or from accidental contamination of feed by chemicals or drugs.

12.1 Regulation of drug residue

Livestock and poultry production depends on drugs and other chemicals to protect animal health. Consumers are protected from adverse effects by regulation of chemicals and drugs and the detection of chemical and drug residues in foods of animals' origin through national agencies (FDA in USA, Veterinary Drug Directorate in Canada, Medicines and healthcare products regulatory agency in UK and others). The codex alimentarius committee on residue of veterinary drugs in foods is subsidiary body of the world health organization (WHO) and the food and agriculture organization (FAO). One of the primary functions of the codex alimentarius is the establishment of the internationally acceptable concentrations of the veterinary drugs in food animal products. Extensive toxicological evaluations of the drugs and its metabolite are required before the drug is approved for use in food-producing animals. Based on the results of toxicity tests, regulatory agencies establish an acceptable daily intake (ADI). The ADI represents a level of daily intake of a chemical which, during an entire life time, appears to be without appreciable risk to the health of the consumer. The ADI is used to determine the maximum concentration of a marker residue in edible tissues, honey, milk or eggs that is legally permitted or recognized as acceptable. These acceptable concentrations are also termed as "tolerances" (USA) or "maximum residue limits" (MRL) (Canada and European union).

12.2 Pharmacokinetics and drug residues

Pharmacokinetics is the science of quantitating the change in drug concentration in the body over time as a function of the administered dose. How a drug or combination of drugs behaves in the body after administration not only is important from therapeutic point of view but is of paramount importance in order to prevent residues in the edible tissues after the disease process has been resolved and the animal is slaughtered. For determining withdrawal times of drug, half-life ($t_{1/2}$) of drug is more relevant. The $t_{1/2}$ of a drug by definition is the time taken for 50% of the drug in the animal to be eliminated from the body. It is calculated by the equation.

$$t_{1/2} = \ln 2 / \text{slope} \text{ or } t_{1/2} = 0.693 / \text{slope} \quad (1)$$

Half-life is influenced by biological factors like volume of distribution and elimination rate. The volume of distribution (V_d) is the quantitative estimate of the extent of the distribution

of the drug in the body and it influence $t_{1/2}$ of the drug. It is proportionality constant relating the concentration of drug in the serum to the total amount of drug in the body.

$$V_d = \text{amount of drug in the body} / \text{serum drug concentration} \quad (2)$$

In addition to V_d , the clearance (Cl) of the drug also play important role in determining the withdrawal time of the drug. Clearance quantitates the efficiency of the elimination process and is defined as the rate of drug elimination from the body relative to the concentration of drug in the serum.

$$Cl = \text{rate of elimination} / \text{Serum drug concentration} \quad (3)$$

The $t_{1/2}$ dependent on two functions: Volume of distribution and clearance. By combining term, an equation can be derived that reflects the influence of V_d and Cl on the $t_{1/2}$ of a drug.

$$t_{1/2} = \ln 2 V_d / Cl \text{ or } t_{1/2} = 0.693 V_d / Cl \quad (4)$$

For an orally or extrvascularly administrated drug withdrawal can be derived as

$$\text{Withdrawal time} = 1.44 \ln C^0 (\text{tolerance}) (t_{1/2}) \quad (5)$$

Where C^0 is the initial concentration of drug in the body derived by ratio bioavailability to V_d .

The above equation is useful to gain a perspective on what the withdrawal time is relative to the terminal half-life. If the drug has a short half-life (eg. penicillin), the withdrawal time is short. However, If a drug (eg. An aminoglycoside) has a prolonged tissue half-life the withdrawal time could be very long. Similarly, a drug with a very low tissue tolerance has a longer withdrawal time.

For lactating dairy cows and goats milk discard times are determined using pharmacokinetic principles. The milk discard or withdrawing time is the time after drug administration when the milk cannot be used for human consumption. This is determined by administering the drug and collecting and analyzing milk until drug concentrations are below the milk tolerance established for that drug. It is based on the half-life of the drug in the milk. Basic drugs like erythromycin have longer discard times than acidic drugs such as penicillin because the former tend to distribute more readily into milk due to pH partitioning phenomenon. Similarly, lipophilic drugs will tend to have longer milk discard times.

13. Conclusion

Food safety is one of the most significant issue faced by livestock owners and consumers of animal derived food. Residues of drugs and chemicals in food of animal origin raise special concern for human safety. Consumer concern about drug residue in animal food has led to reduction in demand in many countries. It has also disturbed international trade of food. Globally, food safety programs are advancing but formal training in drug residue prevention is limited. It is global need that Veterinarians should be acquainted with legal and regulatory issues concerning control of drug and other chemicals residues in food animals. The primary pharmacokinetic parameters used by veterinarians to prevent violative tissue residues are withdrawal time for meat and discard time for milk.

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Unit 405, Office Block, Hotel Equatorial Shanghai
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Phone: +86-21-62489820
Fax: +86-21-62489821