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Unique Pharmacokinetic and Pharmacodynamic Parameters of Antimicrobials in Goats

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Abstract

Pharmacokinetics, the process that involves drug absorption, distribution, metabolism and excretion (ADME) of antimicrobials, determines pharmacodynamic response, that is, what drugs do to the body. Therefore, of all the pharmacokinetic parameters, elimination half-life ($T_{1/2\beta}$), volume of distribution (Vd), maximum plasma concentration (C_{max}) and maximum time reached (T_{max}) are the most important parameters. Hence, the parameters are unique in determining pharmacokinetic and pharmacodynamic response of antimicrobials. However, it is elimination half-life and minimum inhibitory concentration (MIC) that determine the dosing interval of antimicrobials. The dose range of 2.5 mg/kg for gentamicin passing through 4 mg/kg (ciprofloxacin), 4.2 mg/kg (ampicillin L/A), 5 mg/kg (kanamycin, enrofloxacin, gatifloxacin and norfloxacin), 7 mg/kg (mequindox), 10 mg/kg (amikacin, enrofloxacin, lincomycin, pefloxacin, cefpirome, erythromycin and isoniazid), 20 mg/kg (oxytetracycline) and 30 mg/kg (metronidazole) have elimination half-life of 1.2–67.2 h, C_{max} of 0.12–54.4 µg/ml, T_{max} of 0.2–24 h, bioavailability of 16–99.8% and plasma protein binding of 0–80% when administered intramuscularly, intravenously and orally. Human equivalent dose formula could be used to extrapolate human-goat therapeutic doses of antimicrobials. However, some antimicrobials such as sulfadimidine, tulathromycin, oxytetracycline and azithromycin may have high residues in the milk, kidneys, liver, intestines, brain and skeletal muscles and may portend high risk of antimicrobial resistance, hypersensitivity reaction, epidermal necrolysis, Stevens-Johnson syndrome and other adverse drug reactions.

Keywords: pharmacokinetics, pharmacodynamics, goat, tissue residue, human equivalent dose, resistance, receptor, agonism, antagonism

1. Introduction

Antimicrobials are either synthetic or natural products (antibiotics) that are used in killing (bactericidal) or controlling the growth (bacteriostatic) of pathogenic microbes. Sometimes, antimicrobial and antibiotic are interchangeably used. Goats belong to species (caprine) and serve as the source of meat and milk [1], and the money realized from sales meet financial obligations of small- and large-scale goat farmers [2]. There are up to 800 million goats in the world [3]. The economic species of goats spread across the globe are not limited to Teddy, Kilis, Ardi,

West African Dwarf, Black Bengal, Indian native, Murciano-Granadina, Angora, Red Sokoto, Boer and Nubian goats [4–13]. However, the diseases of goats include colibacillosis, salmonellosis, staphylococcosis and streptococcosis, among others [14]. Age, sex, dosage formulation, route of administration and dose of antimicrobials affect pharmacokinetics and pharmacodynamics of antimicrobials in goats [13]. For example, female West African dwarf goats are more sensitive to sulfadimidine than male West African dwarf goats [15]. There are also intraspecies differences in pharmacokinetic and pharmacodynamic parameters of domestic goat (*Capra aegagrus hircus*) such as West African dwarf, Pakistan, Shiba, Netherland dwarf, Nubian, Red cross-breed, Angora, Boer, LaMancha, Oberhasli, Toggenburg as well as wild goats, *Capra aegagrus aegagrus* (bezoar ibex), *Capra aegagrus blythi* (Sindh ibex), *Oreamnos americanus* (mountain goat), *Capra aegagrus chialtanensis* (Chiltan ibex), *Capra aegagrus cretica* (kri-kri), *Capra aegagrus turcmunica* (Turkmen wild goat) and *Capra aegagrus pictus* [15–20]. However, *Capra aegagrus hircus* is the most popular domesticated from their wild progenitor, bezoar (*Capra aegagrus*) [21, 22]. Also, antimicrobials such as sulfonamides, trimethoprim-sulfamethoxazole, aminopenicillins, cephalosporins and quinolones could cause Stevens-Johnson syndrome in humans that eat goat meat which has the drugs residues [23] and tissue residues above threshold (2 ppm) could be found in the skeletal muscle, liver, kidney, milk, brain, intestine, heart and lung of goats which could portend threat to public health [13]. Although goats are domesticated 10,500 years ago, the genomic regions differentiating domestic goats from wild goats are associated to genes of the nervous system, immunity and productivity traits; 20 are common to *Capra* and *Ovis* [24] indicating the possible relevance of pharmacogenomics which is the study of how genes affect animal response to drugs. Because of unprecedented emergence of resistant bacteria, there is a fervent need to develop new veterinary drugs [25] using both in vitro and in vivo data that have been generated from basic, translational and clinical research. Solubility and permeability affect pharmacokinetics of oral formulations of antimicrobials in goats. The formulations are tablet, capsule, solution, suspension, etc.

2. Methodology

Intensive literature search was carried out with a view to identifying various chemical classes, dosage form, routes of administration, therapeutic doses, unique pharmacokinetic parameters such as elimination half-life, volume of distribution, bioavailability, concentration maximum, peak time, plasma concentration, minimum inhibitory concentration and spectrum of activities of various antimicrobials in various breeds of domestic and wild goats. Oral dose formulations of antimicrobials have been classified biopharmaceutically, and pharmacokinetic equations used for calculation of common pharmacokinetic parameters have been highlighted. Information on pharmacodynamic parameters, intraspecies and interspecies scaling, tissue residues, antimicrobial resistance, rehydration therapy and antimicrobial intoxication has been elucidated.

3. Results

Kinetic parameters of some antimicrobial drugs used in treatment of microbial infections in goats, goat-human extrapolated doses of some antimicrobials and half-life and tissue residues and withdrawal periods of some antimicrobials are presented in **Tables 1–3**, respectively.

Chemical class	Name	Route	Dose (mg/kg)	T ¹ / ₂ β (h)	Bioavailability (%)	Cmax (µg/ml)	Tmax (h)	Breed	Spectrum of activity	References
Fluoroquinolone	Levofloxacin	Subcut	1.25	4.67	—	0.33	—	—	Gram-negative	[26]
Aminoglycoside	Kanamycin	i.v.	5	2.8 ± 0.02	—	33.6 ± 5.5	—	Teddy	Gram-negative bacilli	[7, 8]
	Amikacin	i.v.	10	1.94 ± 0.10	—	—	—	Indian native	Gram-negative bacilli	
Fluoroquinolone	Levofloxacin	i.v.	10	4.04 ± 0.24	—	15.51 ± 1.41	—	Bengal	<i>S. aureus</i>	[6, 9, 27, 28]
	Ofloxacin	i.v.	5	6.20 ± 0.23	32.5	0.81 ± 0.00	—	Angora	<i>S. aureus</i>	
	Enrofloxacin	i.v.	5	3.93 ± 0.46	—	15.53 ± 1.31	—	Egyptian native	Wide spectrum of activities	
Aminoglycoside	Gentamicin	i.v., i.m.	5	8.1 ± 1.6	94	—	-	Markhor	Gram-negative spp.	[29]
Fluoroquinolone	Ciprofloxacin	i.v.	4	1.63 ± 0.17	—	4.47 ± 0.33	—	Bengal	<i>Salmonella</i> spp.	[30–32]
	Norfloxacin	i.m.	5	5.24 ± 1.98	66	2.06 ± 0.42	0.77 ± 0.18	Pakistan native	Gram-negative spp.	
	Gatifloxacin	i.v.	5	2.47 ± 0.08	—	—	—		Anaerobes	
Glycopeptide	Lincomycin	i.v.	10	9.99 ± 2.83	—	46.0 ± 7.06	—	—	Bacteria	[33, 34]
		i.m.	10	6.19 ± 0.25	—	5.63 ± 2.5	0.2 ± 0.16		Bacteria	
Macrolide	Tulathromycin	Subcut	25	67.2	—	0.12 ± 0.02	24	—	Bacteria	[35]
Fluoroquinolone	Pefloxacin	i.v.	10	1.2 ± 0.21	—	—	—	—	<i>E. coli</i>	[36]
		Oral	20	2.91 ± 0.50	42	2.22 ± 0.48	2.3 ± 0.7		<i>E. coli</i>	
Cephalosporin	Cefpirome	i.v., i.m.	10	2.09 ± 0.08	75	10.97 ± 0.34	—	Surti	Gram-positive	[37]
Macrolide	Azithromycin	i.v., i.m.	20	45.2	92.2	—	—	—	Bacteria	[38, 39]
	Erythromycin	i.v., i.m.	10	1.41 ± 1.20	98.83	2.99 ± 1.53	—		Bacteria	
Penicillin	Ampicillin (L/A)	i.v.	4.2	1.71	—	0.26	0.04	Ardi	Gram-positive/Gram-negative microbes	[10]
Danoxaline	Mequindox	i.v., i.m.	7	1.8	99.8	11.01 ± 2.94	0.67 ± 0.13	—	Broad spectrum	[40]

Chemical class	Name	Route	Dose (mg/kg)	T ¹ / ₂ β (h)	Bioavailability (%)	Cmax (μg/ml)	Tmax (h)	Breed	Spectrum of activity	References
Tetracycline	Oxytetracycline	i.v., i.m.	20	27.96 ± 11.66	83.2	13.57 ± 5.83	0.46 ± 0.09	Kilis	Broad spectrum	[11]
			10					West African dwarf		
	Isoniazid	Oral	10	2.05 ± 0.72	—	3.71 ± 0.40	3.14 ± 0.19	Teddy	Antituberculosis	[12]
Nitroimidazole	Metronidazole	i.m.	30	5.87	—	54.4	2.0	Nubian	Antiprotozoan; antibacterial	[4]
Cephalosporin	Ceftriaxone	i.m., i.v.	20	1.5–2.03	—	21.51	—	—	Gram-positive	[41]
Fluoroquinolone	Marbofloxacin	i.m.	2	7.2	—	1.9	—	—	Gram-negative	[42]
Key: —, non-available data.										

Table 1.
Kinetic parameters of some antimicrobial drugs used in treatment of microbial infections in goats.

Antimicrobial	Route	Dose of drug (mg/kg)	Weight of goat (kg)	BSA of goat (m ²)	Goat Km (m/kg)	Weight of human (kg)	Height of human (m)	BSA of human (m ²)	Human Km (m/kg)	Translated human dose (mg/kg)
Tulathromycin	Subcut	2.5	20	0.76	0.04	78	1.9	1.96	0.025	4
Erythromycin	i.m., i.v.	10, 15	30	1.00	0.03	78	1.9	1.96	0.025	18
Tylosin	i.m.	15	22	0.81	0.04	72	1.85	1.85	0.026	23
Pefloxacin	i.v.	10	25	0.88	0.04	51.3	1.58	1.42	0.028	14.3
Ciprofloxacin	i.v.	10	30	1.00	0.03	48	1.48	1.32	0.028	10.7
Cefpirome	i.m., i.v.	10	32	1.04	0.03	46.5	1.59	1.36	0.029	10.3
Lincomycin	i.m.	10	50	1.40	0.03	44.8	1.55	1.31	0.029	10.3
Enrofloxacin	i.m.	5	20	0.76	0.04	44	1.63	1.34	0.030	6.7
Norfloxacin	i.m.	5	30	1.00	0.03	35.5	1.46	1.13	0.031	4.8
Gatifloxacin	i.v.	10	20	0.76	0.04	31.4	1.46	1.05	0.033	12.1
Azithromycin	i.v.	20	30	1.00	0.03	43	1.58	1.30	0.030	20
Mequindox	i.m., i.v.	7	30	1.00	0.03	48	1.53	1.35	0.028	7.5
Metronidazole	i.m.	30	33	1.07	0.03	49.3	1.60	1.40	0.028	32
Kanamycin	i.v.	5	30	1.00	0.03	20	1.58	0.87	0.043	3.5
Gentamicin	i.v.	2	20	0.76	0.04	60	1.60	1.56	0.026	3.0
Streptomycin	i.v.	10	30	1.00	0.03	51.3	1.58	1.42	0.028	10.7
Difloxacin	i.m., i.v.	5	50.2	1.41	0.03	55	1.70	1.54	0.028	5.4
Levofloxacin	i.v.	10	20	0.76	0.04	65	1.70	1.68	0.026	15.4
Ofloxacin	i.v.	5	20	0.76	0.04	70	1.50	1.63	0.023	8.7

Antimicrobial	Route	Dose of drug (mg/kg)	Weight of goat (kg)	BSA of goat (m ²)	Goat Km (m/kg)	Weight of human (kg)	Height of human (m)	BSA of human (m ²)	Human Km (m/kg)	Translated human dose (mg/kg)
Ampicillin	i.v.	4.2	55	1.50	0.03	45	1.40	1.25	0.028	4.5
Isoniazid	Oral	10	40	1.21	0.03	30	1.30	0.97	0.032	9.4
Oxytetracycline	i.m., i.v.	20	40	1.21	0.03	64	1.60	1.61	0.025	24
Amikacin	i.m.	10	25	0.88	0.03	56	1.30	1.35	0.024	12.5
Sulfadimidine	i.m.	33.3	10.4	0.49	0.05	60	1.20	0.75	0.0125	66.6

Table 2.
Goat-human extrapolated doses of some antimicrobials.

Antimicrobial	Route	Dose (mg/kg)	T ¹ / ₂ β (h)	Quantity of residues (ppm)	Withdrawal period	Affected organ	Consequence(s)	References
Tulathromycin	Subcut	2.5	61.4 ± 141 days	2.09 ± 1.77	34 days	Kidney	Nephrosis	[5]
Erythromycin	i.v., i.m.	10, 15	—	2.06 ± 0.36	—	Milk	Resistance	[39]
Sulfadimidine	i.m.	100	26.3–41.9 days	1.24–5.68	>30 days	Kidney, liver, brain, skeletal muscle, intestine, heart	Steven-Johnson syndrome, nephrosis	[13]
Tylosin	i.m., i.v.	15	6.8 h	1.70 ± 0.03	2 days	Milk	Possible resistance in kid	[43]
Gatifloxacin	i.v.	5	12 h	2.00	2 days	Milk	Resistance in kid	[32]
Delafloxacin	Subcut, i.m., i.v.	5	4.5–6.4 h	1.2–2.1	>1.5 days	Milk	Resistance in kid	[44]
Levofloxacin	i.v.	10	4.6–7.3 h	14.7–17.0	12.3–42.3 h	Milk	Resistance in kid	[9]
Ceftazidime	i.m., i.v.	10	4.7±1.1 h	2.4–18.3	4 days	Milk	Resistance in kid	[45]

Table 3.
Half-life, tissue residues and withdrawal period of some antimicrobials.

3.1 Biopharmaceutical classification of oral antimicrobials

This is a system of classifying antimicrobials based on aqueous solubility and intestinal permeability. The four major factors being considered in this classification system are dosage form, dissolution rate, solubility and permeability. Hence, antimicrobials are tested in vitro and classified into four classes:

Class 1: High solubility – high permeability

Class 2: Low solubility – high permeability

Class 3: High solubility – low permeability

Class 4: Low solubility – low permeability

All the classes of dissolution can occur in a pH range of 1–2, 4–5 and 6–8 [46]. Nevertheless, administration of highly toxic antimicrobials such as aminoglycosides (e.g. gentamicin) should be monitored since it damages the kidney.

Such drugs are said to have narrow therapeutic range (NTR)

$$= \frac{\text{Minimum toxic concentration (MTC)}}{\text{Median effective concentration (MEC)}}$$

3.2 Pharmacokinetic equations of antimicrobials

Bioavailability, absorption half-life ($T_{1/2\alpha}$), mean absorption time (MAT), mean residence time (MRT), apparent volume of distribution (V_d), volume of distribution, steady state (V_{dss}), area under curve (AUC), area under the first moment curve (AUMC), peak time (T_{max}), elimination half-life ($T_{1/2\beta}$) and systemic clearance (Cl) are the pharmacokinetic parameters commonly determined in all species of animals and humans [7, 9, 47–49]. The most important of all these parameters are elimination half-life, volume of distribution and plasma concentration of the antimicrobials.

The pharmacokinetic process of antimicrobials in goats obeys first-order kinetic (**Figures 1** and **2**) which could be mono-exponential or bi-exponential. The exponential equation commonly used for determination of pharmacokinetic parameters is $CP = A_e^{\alpha t} + B_e^{-\beta t}$. Other equations are:

$$T_{1/2\alpha} = \frac{0.693 \times MAT}{k_a} \quad (1)$$

$$MAT = 1/k_a \quad (2)$$

$$MRT = \frac{AUMC}{AUC} \quad (3)$$

$$V_d = \frac{Cl_b}{\beta} \quad (4)$$

$$AUC = \frac{\text{Dose}}{Cl} \quad (5)$$

$$AUMC = MRT \times AUC \quad (6)$$

$$T_{1/2\beta} = \frac{0.693}{\beta} \quad (7)$$

$$Cl_b = \frac{\text{Dose}}{AUC} \quad (8)$$

However, peak time (T_{max}) and C_{max} can be estimated from the pharmacokinetic graph [47].

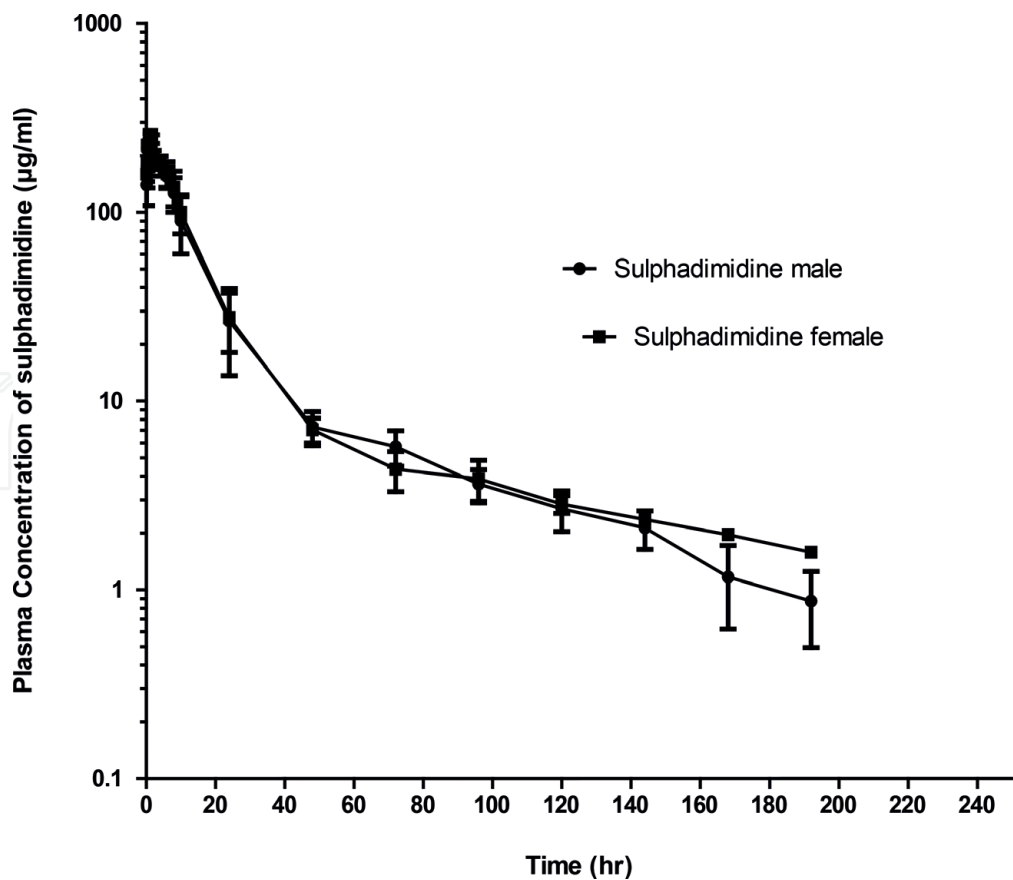


Figure 1.
Mean plasma concentration-time curves of sulfadimidine (100 mg/kg) in male and female WAD goats following intramuscular administration.

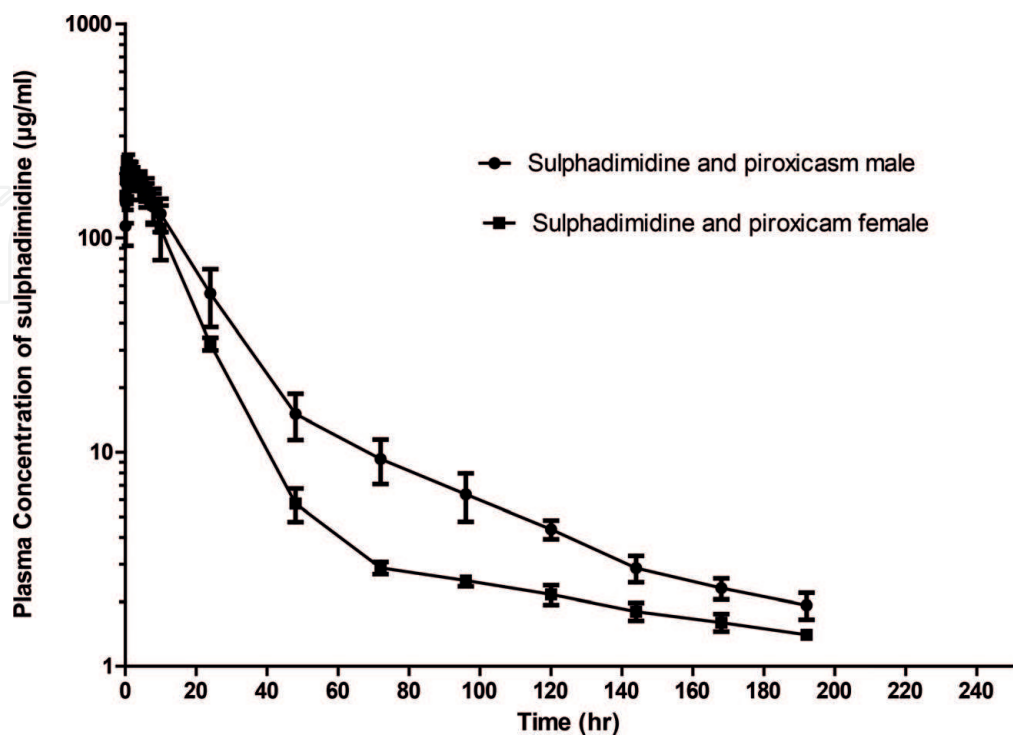


Figure 2.
Mean plasma concentration-time curves of sulfadimidine (100 mg/kg) when co-administered with piroxicam (5 mg/kg) to male and female WAD goats following intramuscular administration.

$$\text{Dosage rate (DR)} = \frac{\text{bioavailability (F)} \times \text{dose (D)}}{\text{dosage interval (DI)}} \quad (9)$$

$$\text{DR} = \frac{\text{plasma concentration (CP)}}{\text{body clearance (Clb)}} \quad (10)$$

$$\text{Infusion rate (Ro)} = \text{plasma concentration, steady state (Cpss)} \times \text{Clb} \quad (11)$$

$$\text{Accumulation index} = \frac{1}{\text{fraction lost per dosing interval}} \quad (12)$$

$$= \frac{1}{1 - \text{fraction left in the body}} \quad (13)$$

$$\text{Loading dose (LD)} = \frac{\text{target Cp} \times \text{Vss}}{\text{F}} \quad (14)$$

$$\text{LD} = \text{maintenance dose (MD)} \times \text{accumulation index (AI)} \quad (15)$$

$$\text{MD} = \frac{\text{DR} \times \text{DI}}{\text{F}} \quad (16)$$

$$\text{Rate of elimination (RE)} = \text{CL} \times \text{concentration} \quad (17)$$

$$\text{Bioavailability (F\%)} = \frac{\text{AUC Oral, Sc, Im} \times 100}{\text{AUCiv}} \quad (18)$$

4. Discussion

4.1 Comparative pharmacokinetics of antimicrobials in domestic goats

Species variations in response to antimicrobials are very important. Various antimicrobials from different chemical classes, their routes of administration, doses, elimination half-life, bioavailability, maximal concentration, peak time, breed and spectra of activity are presented in **Table 1**. The therapeutic doses of fluoroquinolones in goats are 1.2 mg/kg subcut for levofloxacin, 5 mg/kg i.v. (orfloxacin, enrofloxacin, norfloxacin and gatifloxacin) and 20 mg/kg oral (pefloxacin). The elimination half-life (2.8 ± 0.02 h) of kanamycin (5 mg/kg) and half-life (1.94 ± 0.1 h) of amikacin (10 mg/kg) in Teddy and Indian native goat, respectively, show that the disposition kinetics of aminoglycosides in goats is dependent on the dose of drugs. Also, disposition kinetics of antimicrobials in goats could be species dependent. For example, C_{max} (236.3 ± 0.00 µg/ml) of sulfadimidine in West African dwarf (**Figure 1**) is higher than that of Pakistan female goat (6.0 ± 3.0 µg/ml) and Shiba goat (2.14 ± 1.05 µg/ml), respectively [16]. T_{max} of West African dwarf (1.1 ± 0.3 h) is lower than that of Shiba (2.0 ± 1.2 h) and Netherland dwarf (2.0 ± 0.5 h), respectively [18, 19]. But V_d (3.9 ± 0.8 L/kg) in West African dwarf is higher than that of Nubian (0.32 ± 0.0 L/kg), Shiba (0.4 ± 0.2 L/kg) and cross-breed ($0.3\text{--}0.5$ L/kg), respectively [17, 19, 20], suggesting the difference in breed response to antimicrobials. However, half-life of kanamycin (5 mg/kg) was higher in buffaloes (4.35 ± 0.24 h), cow (6.0 ± 0.50 h) and sheep (3.4 ± 0.1 h) than that of goat (2.8 ± 0.2 h), respectively, indicating that goat is the species most sensitive to kanamycin among these species of herbivores. Also, difloxacin is effective at 5 mg/kg [8]. But normal milk reduces the activity of enrofloxacin against *E. coli* [50]. However, $T_{1/2\beta}$ (1.94 ± 0.1 h) of kanamycin for normal goat is lower than the $T_{1/2\beta}$ (3.17 ± 0.13 h) for febrile goat. Maintenance of therapeutic concentration (2 mg/ml) requires a priming dose of 14.73 mg/kg and

maintenance dose of 13.95 mg/kg at an 8-h interval, respectively [8]. Plasma concentration of levofloxacin is higher in healthy goats ($15.51 \pm 1.41 \mu\text{g/ml}$) than mastitis goats ($12.48 \pm 1.36 \mu\text{g/ml}$). This plasma concentration does not affect levofloxacin elimination [9].

Since various brands of enrofloxacin have different pharmacokinetic parameters such as half-life (3.93 ± 0.46 ; 4.04 ± 0.53 ; 4.56 ± 1.24 h) and plasma concentrations (15.53 ± 1.31 ; 6.75 ± 0.56 ; $10.40 \pm 2.65 \mu\text{g/ml}$) [28], dosage formulations may have sufficient effects on pharmacokinetics and pharmacodynamics of aminoglycosides. Serum concentration of gentamicin (5 mg/kg) was maintained at $1.5\text{--}12 \mu\text{g/ml}$ for a period of 6 h. But gentamicin (2.5–3.0 mg/kg i.m.) every 8 h is therapeutically useful with less risk of nephrotoxicity [29], as daily intravenous administration of 4 mg/kg is effective for 36 h in the treatment of systemic and urinary tract infections caused by Gram-negative pathogens in goats [30]. Therefore, optimal dosage regimen, bioequivalence and kinetic parameters of antimicrobials are of clinical importance [31]. Elimination half-life, C_{max} and T_{max} of intramuscular enrofloxacin (2.5 mg/kg) are 5.39 ± 0.96 h, $1.14 \pm 0.09 \mu\text{g/ml}$ and 0.83 ± 0.13 h, respectively [51]. Gatifloxacin (5 mg/kg) provided minimum inhibitory concentration (MIC) of $0.1\text{--}2 \mu\text{g/ml}$ for susceptible microorganisms between 6 and 12 h in healthy and febrile goats, respectively [32]. Elimination half-life (3.98 ± 0.18 h), C_{max} ($9.24 \pm 1.2 \mu\text{g/ml}$), MRT (4.13 ± 0.16 h), V_{dss} (1.22 ± 0.06 L/kg) and Clb (0.24 ± 0.01 l/h/kg) of enrofloxacin (5 mg/kg) have been reported [6]. The V_{d} (3.35 ± 0.45 L/kg), Clb (0.28 ± 0.03 l/h/kg) and $T^{1/2}_{\beta}$ (9.99 ± 2.83 h) suggest long persistence of lincomycin in goat as it can be repeated every 24 h with MIC ($0.6 \mu\text{g/ml}$) for treatment of febrile bacterial infections in goats [33]. But intramuscular lincomycin can be administered every 12 h [34].

Vancomycin was initially active against methicillin-resistant *Staphylococcus*, but presently vancomycin-resistant *Staphylococcus* has emerged, and vancomycin-resistant *Enterococcus* has also emerged due to its usage as feed additive. Hence, prophylactic use of antibiotics should be highly reduced [52]. Concentration of pefloxacin ($0.25 \mu\text{g/ml}$) was maintained in plasma for 6–10 h after oral or intravenous administration. Therefore, intravenous pefloxacin (20 mg/kg) every 6 h or thrice orally is effective against sensitive pathogenic microbes in goats [36]. But intravenous dose (10 mg/kg) of ciprofloxacin with $T^{1/2}_{\beta}$ (2.72 ± 1.04 h), MRT (3.33 ± 1.42 h), V_{dss} (3.37 ± 0.8 l/kg) and Clb (19.59 ± 9.05 ml/min/kg), respectively, should be administered every 12 h [53]. Cefpirome (10 mg/kg) every 12 h is useful when administered intravenously in goats. It is 19.9% plasma protein bound [37] and so may compete weakly with other plasma-binding drugs such as sulfadimidine, warfarin, non-steroidal anti-inflammatory drugs and barbiturates. The long half-life of azithromycin after intravenous (45.2 h) and intramuscular (32.5 h) administration and MRT of 40.1 h and 60.3 h and bioavailability of 92.2% [38] show that the drug could be administered every 2 and 3 days, respectively. But half-life (67.2 h) of tulathromycin (25 mg/kg) indicates that the withdrawal period of tulathromycin may be long and there may not be a need for repeated doses of the drug. But elimination of erythromycin is higher in lactating goats (3.18 ± 1.32 h) than non-lactating goats (1.41 ± 1.20 h) [39] signifying that erythromycin is quickly removed from the body of non-lactating goats. MIC of erythromycin against *Staphylococcus aureus* was 0.50 and $0.75 \mu\text{g/ml}$ [54], respectively. Tylosin (10–15 mg/kg) was administered to goats both intramuscularly and intravenously. The intramuscular bioavailability was 72.6%, and serum protein binding was 37.6%, C_{max} ($2.38 \mu\text{g/ml}$), V_{d} (1.7 L/kg), $T^{1/2}_{\beta}$ (3.04 h), T_{max} (4.19 h) and Clb (6.8 ml/kg/min), respectively. Hence, tylosin should be injected every 14 h [43]. Gentamicin (4 mg/kg), amikacin (10 mg/kg), tobramycin (5 mg/kg), kanamycin (10 mg/kg) and apramycin (20 mg/kg) may have synergistic or additive antibacterial activity [55]. Intramuscular

metronidazole can be administered to goats at 10 mg/kg body weight every 12 h [4]. Oxytetracycline (10 mg/kg), ampicillin (20 mg/kg) and combination of trimethoprim (20 mg/kg), sulfamethazine (50 mg/kg) and sulphamethyl phenazine (50 mg/kg) are effective in treatment of ehrlichiosis [56]. But extensive and very wide use of antimicrobial agents in goats may portend very high risk of resistance [57]. Therefore, each antimicrobial must be studied on species basis for effective and safe use for animal well-being and public safety in terms of animal product consumption and human/animal drug resistance [3].

4.2 Pharmacokinetics of antimicrobials in wild goats

Although the information on pharmacokinetics of wild goats is rare, allometric scaling can be applied for extrapolation of some parameters including Vd and Cl except $T_{1/2\beta}$ [58]. Ceftazidime (10 mg/kg) administered to Creole goat showed high serum concentration, good penetration and high bioavailability of the drug [45]. But cephalexin (10 mg/kg) administered (subcut, i.m. and i.v.) to *Lama glama* showed high bioavailability of 72% (i.m.) and 89% (i.v.), respectively. The MIC₉₀ values of cephalexin against coagulase-positive staphylococci and *E. coli* were 1.0 µg/ml and 8.0 µg/ml, respectively [59]. But MIC₉₀ value (0.01–0.1 µg/ml) of ceftazidime against *E. coli*, *Salmonella* species, *Pasteurella haemolytica* and *P. multocida* [45] shows that ceftazidime is more active and efficacious than cephalexin, which can be administered 8 mg/kg i.m. or subcut every 12 or 24 h, respectively [59]. Other modes of administration such as ballistic implants and impregnated beads can be employed for some antimicrobials to avoid frequent administration as seen in cefovecin with very long half-life in dogs and cats, allowing a dosing interval of 14 days [60, 61]. This strategy may reduce the chance of resistance by microorganisms against antimicrobials. For example, an amoxicillin formulation with half-life of 130 h can be administered every 6 days, and ceftiofur with half-life of 37 h can be administered every 2 days in goats [62]. Orbifloxacin administered to Mehsana goat (2.5 mg/kg i.v.) with $T_{1/2\beta}$ (8.63 ± 0.13 h), Vdss (2.99 ± 0.04 l/kg), MRT (21.07 ± 0.8 h) and bioavailability (155.5%) showed antimicrobial activity against *E. faecalis*, *S. epidermidis*, *S. intermedius*, *S. aureus*, *S. pyogenes*, *E. coli*, *S. typhimurium*, *S. typhi*, *S. enterica*, *Shigella flexneri*, *K. pneumoniae*, *E. aerogenes*, *P. aeruginosa*, *P. mirabilis*, *Pasteurella* species, *Mycoplasma* species and *Mannheimia haemolytica* [63].

4.3 Pharmacodynamics of antimicrobials

Pharmacokinetics determine maximal therapeutic effect that depends on plasma drug concentration, drug receptors, health status and co-administration of antimicrobial with another drug that shares same or different binding receptors. Slowly eliminated and accumulated antimicrobials are least compared by poor dosing interval [64]. The maximal effect of antimicrobials is dependent on molecule-receptor interaction and drug-affinity response. Therefore,

$$\text{Drugs (D)} + \text{receptor (R)} \rightleftharpoons \frac{k_1 \text{DR}}{k_2} \quad (19)$$

$$\text{Affinity constant (Kaff)} = \frac{k_1}{k_2} \quad (20)$$

$$\text{Kaff} = \frac{1}{\text{ED}_{50}} \quad (21)$$

However, antimicrobial treatments can be monitored as follows:

$$\text{Dose}(\text{new}) = \frac{\text{Cpss}(\text{measured})}{\text{Cpss}(\text{desired})} \times \text{Dose}(\text{previous}) \quad (22)$$

But Cpss is achieved when antimicrobial is administered repeatedly at different time intervals.

$$\text{Therapeutic index (TI) is defined as a ratio of } \frac{\text{Lethal dose fifty (LD50)}}{\text{Effective dose fifty (ED50)}} \quad (23)$$

$$\text{Effective dose (ED)} = \frac{\text{CL} \times \text{effective concentration (EC)}}{\text{Bioavailability (F)}} \quad (24)$$

However, when the body weight of goat is reduced by diarrhea or intoxicated by antimicrobials, there may be a need for fluid infusion to maximize balanced pharmacokinetic/pharmacodynamic process of antimicrobials. Clinical correlates of weight loss as a measure of dehydration (>5–12%) must be considered.

$$\text{Drops/minute} = \frac{\text{volume of infusion (ml)}}{\text{time of infusion (min)}} \times \text{drop factor (drops/ml)} \quad (25)$$

$$\text{Infusion rate (IR)} = \text{drug dose} \times \frac{1}{\text{drug conc}} \times \text{drop factor} \quad (26)$$

Only half of calculated deficit should be administered in 1–2 h. Half replacement in 4–6 h is safer and should be completed in 2 days [65]. Isotonic solutions such as 5% dextrose and 0.9% normal saline can be administered via all routes. But hypotonic and hypertonic solutions should be administered intravenously to avoid tissue reaction.

Weighted AUC approach accounts for a more powerful PK/PD link and reveals uniqueness outcome of therapeutic indices and problems of antibiotic resistance [66]. A combination of ampicillin/sulbactam (20 mg/kg) in ratio 2:1 was administered to goat with elimination half-life of ampicillin (0.71 ± 0.12 h), and sulbactam (1.02 ± 0.36 h) shows that the preparation could be administered at the same dosing rate in both sheep and goats [67]. Also, intramuscular dose (2 mg/kg) of cefquinome (Cobactan 2.5%) daily yielded effective MICs against a variety of susceptible pathogenic microbes of goat including *Micrococcus luteus* [68]. Serum concentration and AUC integrated with MIC values can predict clinical success. The efficacy of macrolides, penicillins and tetracyclines is determined by the length of time, the serum concentration exceeds the MIC of a pathogenic microbe. But fluoroquinolones, aminoglycosides and metronidazole have concentration-dependent bactericidal activity [69]. The ratio of C_{max}/MIC indicates potential of antibacterial activity. Amikacin has the lowest MIC₉₀, whereas kanamycin has the highest [55]. Co-administration of two or more drugs could also affect pharmacokinetics and pharmacodynamics of a drug. For example, West African dwarf goats are more sensitive to sulfadimidine co-administered with piroxicam (Figure 2) [15].

4.4 Intraspecies and interspecies scaling of antimicrobials in goats

Variation is an important factor in development of antimicrobials for all species of animals including wild and domestic goats. The problems encountered are how to scale up the pharmacokinetic data from animals to human and how to extrapolate in vitro data to in vivo data for efficacy and safety [70]. There is no enough data on

toxicological effects of antimicrobials in goats. Hence, several extrapolations are necessary in order to arrive at safe therapeutic and toxic doses [71]. The effective therapeutic doses of some antimicrobials translated from goats to human are given in **Table 2**.

The formulas used for calculation of extrapolated doses are as follows [13, 72, 73].

$$\text{Human equivalent dose (HED)} = \frac{\text{animal dose} \times \text{animal Km}}{\text{human Km}} \quad (27)$$

$$\text{Metabolism constant (Km)} = \frac{\text{body surface area}}{\text{body weight}} \quad (28)$$

$$\text{But human body surface area (BSA)} = H^{0.528} \times W^{0.528} \times K \quad (29)$$

whereas H = height, W = weight and K = constant.

But goat's BSA = $W^{0.67} \times 10^{-3}$ and dosimetric adjustment factor (DAF) is body weight of goat over body weight of humans and can be scaled up to 0.25, 0.33 and 0.58. However, body weight exponent of 0.67 and 10^{-3} safety factor should be applied to goat, and the exponent of 0.528 should be applied to human weight and height, respectively [72, 74].

4.5 Antimicrobial tissue residues in goats

Tissue residues of some antimicrobials above recommended thresholds are of public health importance. The presence of sulfadimidine residues (>0.1 ppm) in the liver, kidney, skeletal muscle, spleen, lung, brain and heart after administration of the drug (100 mg/kg) shows that the withdrawal period is longer than 30 days. Hence, sulfadimidine is not easily excreted in West African dwarf goats [13]. This may be due to the presence of desamino-sulfonamide, a sulfadimidine metabolite [75] which is eliminated slowly, thereby increasing the withdrawal time [76]. Lack of adequate water to dilute crystals of sulfadimidine in the kidney can lead to crystalluria that can consequently cause nephrosis in the affected animals [44], and consumptions of meats with high residues of sulfadimidine can cause Steven-Johnson syndrome in sensitive humans who may be slow or fast acetylators [13, 23]. Based on the tissue tolerance limit in cattle (5 ppm), the withdrawal period for tulathromycin is 19 days in cattle and 34 days in goat when administered subcutaneously [5]. The quantity of erythromycin residues ($2.06 \pm 0.36 \mu\text{g}$) is above the recommended threshold and may portend risk to public health. The bioavailability of tylosin in goat is $72.6 \pm 2.3\%$, and its withdrawal period (48 h) [43] shows that the higher the bioavailability, the lower may be the withdrawal period in milk. Residues of antimicrobials in various tissues are presented in **Table 3**. A kid that feeds on milk with residues of antimicrobials may be vulnerable to resistance of microorganisms against the antimicrobials.

4.6 Antimicrobial resistance

Goats are exposed to antimicrobials via prevention, treatment of diseases and growth promotion. This has caused the emergence of resistant *Salmonella*, *Campylobacter*, *Pasteurella*, *Actinobacillus*, *Enterococcus* and *Escherichia* species. The resistance is transferred by genes. But good and improved management practices and increased use of vaccines and probiotics could minimize emergence and spread of resistance genes [77]. Off-label use of antimicrobials in goats could also contribute to emergence of resistance. Meanwhile, lack of official-generated data on consequences of extra-label use of drugs in goats cannot rule out its potential risks to goats

and other species of animals [78]. However, T-phage, transposon and integrin are used for resistance gene transfer. Unfortunately, the worldwide consumption of antimicrobial drugs is increasing, and the manufacturing industries are not keeping pace. The worst of it at the moment is the emergence of superbugs and super drugs. Therefore, there is a need for green antibiotics to minimize the chance of resistance [79].

4.7 Determination of creatinine and glomerular filtration rate as indices of renal function in goats

Kidneys are responsible for water-electrolyte balance in the body, usually affected by activity-rest rhythm under hormonal influence. The diurnal changes are useful in chronobiology and chronopharmacology [80]. Many xenobiotics including antimicrobials are toxic to the kidney, and renal impairment can be assessed using creatinine clearance which is physiologically, pharmacologically and toxicologically related to body weight, clearance, volume of urine creatinine, plasma creatinine, serum creatinine, urine volume, glomerular filtration rate, creatinine clearance, creatinine half-life and depuration [81]. The plasma creatinine of Boer-Cross (0.60 mg/dl), Nubian (0.55 mg/dl) and Spanish (0.57 mg/dl) goat have been reported [82], whereas creatinine value (1.03–1.24 mg/dl) has been reported for healthy captive, Persian wild goat [83]. Area under curve could be used to determine creatinine clearance and plasma clearance as demonstrated in the equations given below [81].

$$\text{Dose (D)} = \text{AUC} \times [\text{CrCl} + 25] \quad (30)$$

$$\text{Pcl} = \text{CrCl} + 25 \quad (31)$$

$$\text{CrCl} = \text{Pcl} - 25 \quad (32)$$

$$\text{GFR} = \frac{14616.8}{\text{CrCl}/2} \quad (33)$$

$$\text{Depuration (Dep)} = \frac{\text{Ucr}}{\text{Pcr}} \quad (34)$$

$$\text{Serum creatinine (Scr)} = \frac{\text{Ucr}}{1440} \times 1000 \quad (1000 \text{ ml} = 1 \text{ l}) \quad (35)$$

$$\text{Creatinine clearance (CrCl)} = \frac{\text{Ucr}}{\text{Pcr}} \times 144 \quad (36)$$

For example, paracetamol reduced glomerular filtration rate and induced less urinary excretion of isoniazid. Also, renal handling of isoniazid involved glomerular filtration, back diffusion and active tubular secretion [84]. Glomerular filtration rate which is a function of creatinine clearance can be affected by environmental and genetic factors as may be seen in native Pakistan goats administered ampicillin (20 mg/kg) with renal clearance of 0.08 ml/min/kg [85]. Hence, GFR is lower in Pakistan native than the foreign goats [86] unlike renal handling of marbofloxacin in Lohi sheep that involves both glomerular filtration and active tubular secretion [87] indicating that environment has physiological effects on various breeds of goats. This agrees with Bergmann's rule which states that light animals tend to live in hot regions of the world as opposed to fatty animals that tend to live in cold regions [88]. Since 8% of total body weight determines total blood volume, red cell volume and plasma volume could also be determined from hematocrit as indicated in the equation given below [89].

Total blood volume = plasma × 100/100–hematocrit (37)

Long-time administration of sulfadimidine over a period of 1 week may cause hemolysis leading to anemia [90]. Hence, the formula can be used to determine anemia and plasma deficit in goats, photos 1-46 [1, 2, 21, 22, 24].





(22)



(23)



(24)



(25)



(26)



(27)



(28)



(29)



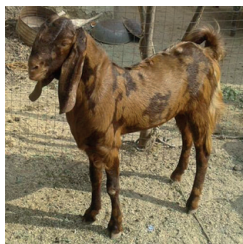
(30)



(31)



(32)



(33)



(34)



(35)



(36)



(37)



(38)



(39)



(40)



(41)



(42)



(43)



(44)



(45)



1, Abergelle goat; 2, Afar goat; 3, African pygmy goat; 4, Altai mountain goat; 5, American Alpine doe; 6, Anglo Nubian goat; 7, Angora goat; 8, Ardi goats in the Arabian Peninsula; 9, Attappady black goat; 10, Babrbari-goat-breed; 11, Beetal-South Asia; 12, Black Bengal goat; 13, Black Oberhasli; 14, Bosque Valley Boer goats; 15, British primitive (Feral goat); 16, Dairy goat; 17, Dutch Toggenburger; 18, Eid-goat; 19, Indian Boer male goat; 20, Italian Adamello blond; 21, Kalahari-red-goat; 22, Marciano-Granadina; 23, Markhor wild goat; 24, Markhor-Pakistan; 25, Murciana goat; 26, Nederlandse Landgeit; 27, Nigeria West African dwarf goat; 28, Nubian blackgold goat; 29, Nubian-Ryan-Somma; 30, Oberhasli goats; 31, Osmanabadi goat; 32, Pakistan Bakra goat; 33, Paaltu Bakri-Nashik goat; 34, Shiba goat; 35, Pure-white-Tappra-teddy-male-goat; 36, Saanen-goat-in-Pakistan-Urdu; 37, Sangamneri-South Asia pro-poor; 38, Shatner goat; 39, Sirohi-male-kid-goat; 40, Sojat-goat; 41, Sokoto Red goat; 42, Teddy-tapra-bakra-goat; 43, Toggenburgerbok goat; 44, Toggenburg-Nigerian-dwarf-Oberhasli-goat; 45, Valachian goat; 46, White Barbari-goat.

5. Conclusion

Pharmacokinetic, pharmacodynamic, intraspecies and extraspecies scaling are some parameters that can affect physiological functions of antimicrobials in goats. Lack of judicious and extralabel use of antimicrobials in goats could cause high tissue residues and development of resistance by susceptible microorganisms against the antimicrobials in both goats and humans. Tissue residues of sulfadimidine may cause Stevens-Johnson syndrome in the vulnerable individuals. Dehydrated goats may be more susceptible to antimicrobial toxicity. GFR can be used to assess the level of kidney damage caused by antimicrobials, and rehydration therapy is useful in dissolution of antimicrobial crystals formed in the kidney. In case of fervent need for extralabel use of antimicrobials, the relevant formulas reported herein could be used to translate goat dose to human dose and vice versa.

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