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Effect Of Oxytetracycline On The Pharmacokinetics Of Sulphadimidine In West African Dwarf Goat

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Abstract
Background*: Combination therapy is a common practice in both veterinary and human medicine, aimed at achieving synergism and enhancing therapeutic outcomes. This study aims to determine the effect of a single dose of oxytetracycline (10 mg/kg body weight) on the pharmacokinetics of sulphadimidine administered at a single dose of 100 mg/kg body weight in West African Dwarf (WAD) goats.*
Materials and Methods*: Eight healthy WAD goats, aged 9 to 10 months and weighing between 11 and 13 kg, were obtained from smallholder farmers in Makurdi town and divided into two groups of four animals each. A two-phase parallel study design was employed. The goats in Group One received sulfadimidine alone at a dose of 100 mg/kg body weight administered in the right gluteus muscle; in contrast, the goats in Group Two received sulfadimidine at the same dose concurrently with oxytetracycline at a dose of 10 mg/kg body weight administered in the left gluteus muscle.*
Results*: The kinetic profile for the group receiving only sulphadimidine demonstrated significantly elevated values for the elimination half-life constant (β) at 0.11 ± 0.02 h ¹, elimination half-life (T1/2β) at 8.02 ± 2.48 h, volume of distribution (Vd) at 9.41 ± 2.07 L/kg, and mean absorption time (MAT) at 1.53 ± 0.25 h, in comparison to the group that was administered both sulphadimidine and oxytetracycline, which had values of β at 0.09 ± 0.01 h ¹, T1/2β at 7.94 ± 0.89 h, Vd at 9.02 ± 0.32 L/kg, and MAT at 0.70 ± 0.10 h.*
Conclusion*: The use of sulphadimidine alongside oxytetracycline led to notable alterations in the mean absorption time (MAT), elimination half-life (T1/2β), and volume of distribution (Vd) for sulphadimidine. This combination resulted in elevated serum levels being sustained for an extended duration. Consequently, it can be inferred that oxytetracycline has a synergistic effect with sulphadimidine, and it is advisable to use both medications together.*

Keywords:*Oxytetracycline, Combination therapy, Sulphadimidine, Kinetic profile*

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I. Introduction

Sulphadimidine, also known as sulphamethazine, is a sulphonamide antibacterial agent widely used in veterinary medicine (Agbo *et al*., 2024; Pandey *et al*., 2020; EFSA BIOHAZ PANEL, 2021). Its broad spectrum of activity against various Gram-positive and Gram-negative bacteria has established its utility in treating a range of infections (Melissa, 2024). Historically, sulphadimidine has been employed to treat various infections, including respiratory and gastrointestinal infections. In veterinary medicine, it remains a mainstay for treating bacterial and certain protozoan infections in animals (Spoo and Reviere, 2001).

Oxytetracycline is a broad-spectrum antibiotic that belongs to the tetracycline group and plays a significant role in livestock management (Mark, 2016; Katakweba*et al*., 2012; Olufemi and Agboola, 2009). Its application spans various animal species, effectively addressing a range of bacterial infections. This antibiotic is effective against a wide variety of bacteria, including both Gram-positive and Gram-negative organisms (Ezeibe*et al*., 2004). It is commonly used to treat respiratory infections, such as pneumonia, as well as infections affecting the digestive tract, urinary tract, and other body systems.

The combination of sulphadimidine and oxytetracycline has been clinically used in the treatment of animal diseases. Combining these two drugs in livestock potentially offers a broad spectrum of antibacterial activity, as both are bacteriostatic and have different mechanisms of action. This combination can enhance their effectiveness against a wide variety of bacterial and protozoan infections. It is particularly advantageous in cases where the causative pathogen is unknown or when mixed infections are present. Therefore, this study was conducted to determine the effect of oxytetracycline on the pharmacokinetics of sulphadimidine in West African Dwarf goats.

II. Materials And Methods

Reagents

Trichloroacetic acid (TCA) (Guangdong, China), sodium nitrite (Kermel, China), Sulphamic acid (BDH Chemicals, England), 8-hydroxyquinoline (Sinopharm, China), and sodium hydroxide (Qualikems, India).

Drugs

Sulphadimidine sodium (Shijiazhuang Guanghua Pharmaceutical Co., Ltd., China) and Oxytetracycline (Ashish Life Science Pvt. Ltd., Maharashtra, India)

Experimental Design and Drug Administration

Eight healthy West African Dwarf (WAD) goats, aged 9 to 10 months and weighing between 11 and 13 kg, were procured from breeders within the Makurdi metropolis and divided into two groups of four animals each. Prior to the commencement of the study, all animals were examined for any apparent clinical signs. They were fed a diet of pasture and concentrate, with water provided ad libitum. All animals were vaccinated, dewormed, and acclimatized to their new environment. The handling of the animals adhered to the international guiding principles for biomedical research involving animals, as outlined by the International Council for Laboratory Animal Science (ICLAS) and the Council for International Organizations of Medical Sciences (CIOMS) in 2012.

A parallel study design utilizing random selection of subjects was employed. The goats in Group One received sulfadimidine alone at a dosage of 100 mg/kg body weight administered to the right gluteus muscle. In contrast, the goats in Group Two received sulfadimidine at the same dosage of 100 mg/kg body weight on the right gluteus muscle, concurrently with oxytetracycline at a dosage of 10 mg/kg body weight administered to the left gluteus muscle.

Blood Sample Collection

Pre-treatment blood sampling (2 ml) was conducted in each goat before medication, with additional samples collected at fixed intervals: 15, 30, and 45 minutes, as well as 1, 2, 4, 6, 8, 10, 12, 24, and 48 hours after the administration of the drug preparation. Blood samples were immediately centrifuged at 3,000 × g for 10 minutes, after which the serum was recovered, labeled, frozen, and stored at -20°C until analysis.

Determination of Sulphadimidine in Serum

The serum concentration of sulphadimidine was determined using a modified chemical assay method as described by Nagaraja *et al*. (2007). This method is based on the diazotization of sulphadimidine, followed by coupling with 8-hydroxyquinoline (Sinopharm, China) in an alkaline medium, resulting in red-colored products with an absorption maximum at 500 nm, measured using a UV-visible spectrophotometer (752N, 200-1000 nm).

Calculation of Pharmacokinetic Parameters

The pharmacokinetic analysis of the serum concentrations was conducted using the pharmacokinetic software 'PC Modfit V7.8'. The micro (α, β) constants were determined from all the plotted graphs generated from the data.

Statistical Analysis

Serum concentrations and pharmacokinetic parameters were presented as the mean ± standard error of the mean (SEM) and analyzed using a paired Student's t-test with GraphPad Prism 5.03 for Windows at a 5% level of significance.

III. Results

The mean serum concentrations of sulphadimidine alone and in combination with oxytetracycline in WAD goats are presented in Table 1. The mean serum concentration of sulphadimidine alone was 59.18 µg/ml, while the concentration for the combination of sulphadimidine and oxytetracycline was 42.77 µg/ml at 0.25 hours. These serum concentrations increased until peak values of 85.18 µg/ml and 105.89 µg/ml were reached in the sulphadimidine alone group and the combination group with oxytetracycline at 2 hours and 1 hour, respectively. The peak serum concentrations subsequently decreased, and at 48 hours post-drug administration, the serum concentrations were 3.38 µg/ml in the sulphadimidine alone group and 1.44 µg/ml in the combination group with oxytetracycline.

On the other hand, serum concentrations were significantly lower ($p < 0.05$) at 6 hours and 10 hours in the sulphadimidine-only group compared to the group that received a combination of sulphadimidine and oxytetracycline.

Table 1: Mean serum concentration of sulphadimidine and its combination with oxytetracycline (n=4), Mean±sem

Time (h)	Sulphadimidine alone ()	Sulphadimidineand Oxytetracycline (	P-value
0.250	59.18	42.77	P<0.05
0.500	69.8211.90	68.933.56	p>0.05
0.750	70.9513.79	86.495.74	p>0.05
1.000	82.3218.50	105.893.98	p>0.05
2.000	85.1822.48	91.554.76	p>0.05
4.000	75.0419.09	102.217.71	p>0.05
6.000	63.476.77	91.384.79	P<0.05
8.000	53.903.18	63.9611.05	p>0.05
10.000	41.293.54	58.032.11	P<0.05
12.000	33.745.74	28.598.09	p>0.05
24.000	17.846.80	6.360.97	P<0.05
48.000	3.381.94	1.440.46	p>0.05

The serum concentration of sulphadimidine plotted semi-logarithmically against time after intramuscular administration in both groups is illustrated in figure 1. The figure reflects a 2 compartmental open model.

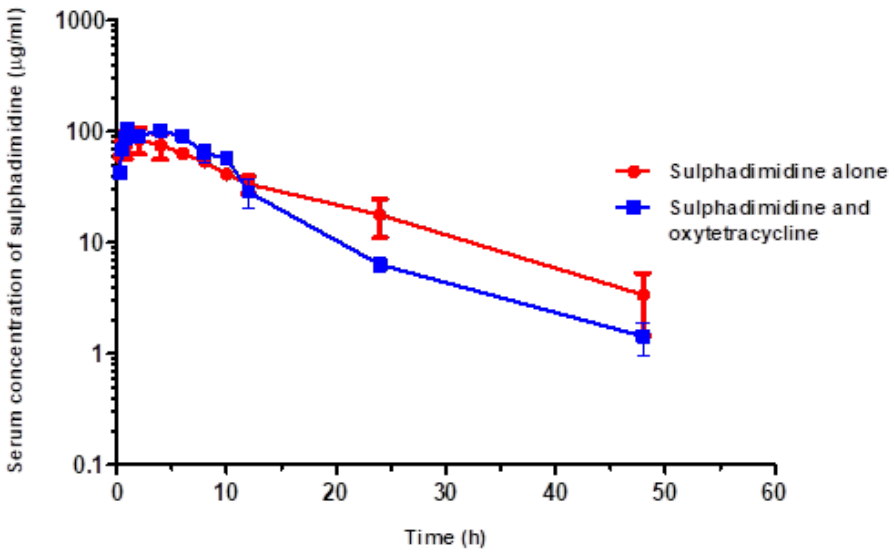

Fig.1 Mean semi-log serum concentration-time curve of sulphadimidine alone and its combination with oxytetracycline.

The pharmacokinetic profile of sulphadimidine in both groups is presented in Table 2. The kinetic profile in the sulphadimidine-only group, including the elimination half-life constant (β) (0.11 ± 0.02 h^{-1}), elimination half-life (T1/2β) (8.02 ± 2.48 h), volume of distribution (Vd) (9.41 ± 2.07 L/kg), and mean absorption time (MAT) (1.53 ± 0.25 h), was significantly higher compared to the values in the group that received sulphadimidine and oxytetracycline concurrently: β (0.09 ± 0.01 h^{-1}), T1/2β (7.94 ± 0.89 h), Vd (9.02 ± 0.32 L/kg), and MAT (0.70 ± 0.10 h). Other kinetic parameters, such as Tmax, Cmax, AUC - , AUC -∞, AUMC - , clearance (Cl), mean residence time (MRT), α, and T1/2α, did not show significant differences ($p > 0.05$) between the two groups.

Table2: Kinetic profile of sulphadimidine and its combination with oxytetracycline, n=4, Mean±sem

Profile	Sulphadimidine	Sulphadimidine andOxytetracycline	p-value
Tmax (h)	1.06±0.33	2.50±0.87	p>0.05
Cmax (h)	88.55±13.24	108.85±4.88	p>0.05
α (h^{-1})	0.82±0.13	1.41±0.02	p>0.05
t1/2α (h)	0.94±0.18	0.50±0.01	p>0.05
MAT (h)	1.53±0.25	0.70±0.10	P<0.05
AUC_{0-t} (µg/ml.h)	1095.81±208.18	1263.19±58.72	p>0.05
$AUC_{0-\infty}$(µg/ml.h)	1145.88±235.46	1281.40±64.73	p>0.05
$AUMC_{0-48}$(µg/ml.h^2)	13493.12±5023.26	11070.77±854.15	p>0.05
β (h^{-1})	0.11±0.02	0.09±0.01	P<0.05
$T_{½\beta}$(h)	8.02±2.48	7.94±0.89	P<0.05
CL (L/kg/h)	1.07±0.42	0.81±0.08	p>0.05
MRT (h)	12.42±4.25	9.44±0.59	p>0.05
Vd (L/kg)	9.41±2.07	9.02±0.32	P<0.05

IV. Discussion

This study was conducted to determine the effect of oxytetracycline (10 mg/kg) on the pharmacokinetic profile of sulphadimidine (100 mg/kg) following a single-dose administration of both drugs in West African Dwarf (WAD) goats. The administration of sulphadimidine alone, as well as its combination with oxytetracycline, resulted in measurable blood levels of sulphadimidine for 48 hours (Table 1). The elimination of sulphadimidine in both groups conforms to a two-compartment open model.

Tmax refers to the time at which the maximum drug concentration is achieved. A Tmax of 1.06 ± 0.33 hours was observed in the group administered sulphadimidine alone, while a Tmax of 2.5 ± 0.87 hours was noted in the group that received both sulphadimidine and oxytetracycline. In another study involving sulphadimidine in West African Dwarf (WAD) goats, a Tmax of 1.62 ± 0.20 hours was reported (Agbo *et al.,* 2019a). Cmax denotes the maximum drug concentration. In goats treated with sulphadimidine alone, a Cmax of 88.55 ± 13.24 µg/ml was achieved, whereas a Cmax of 108.85 ± 4.88 µg/ml was reached in goats treated with both sulphadimidine and oxytetracycline. Additionally, a Cmax of 103.59 ± 7.56 µg/ml was obtained in another study where sulphadimidine was administered alone (Agbo *et al*., 2019b).

Absorption half-life refers to the duration required for fifty percent of an administered drug to be absorbed into the bloodstream. In a study, the absorption half-life was found to be 0.94 ± 0.18 hours in the group that received sulphadimidine alone, compared to 0.50 ± 0.01 hours in the group that received both sulphadimidine and oxytetracycline concurrently. Additionally, a T1/2α of 1.58 ± 0.37 hours was recorded in another experiment involving WAD goats (Akogwu*et al*., 2017).

Mean absorption time (MAT) refers to the average duration a drug remains at the site of administration before being absorbed into the bloodstream. In a study involving goats, the MAT for the group administered both sulphadimidine and oxytetracycline was significantly shorter ($p < 0.05$) at 0.50 ± 0.01 hours compared to the group that received sulphadimidine alone, which had a MAT of 1.53 ± 0.25 hours. This suggests that oxytetracycline may enhance the absorption rate of sulphadimidine from the site of administration.

The area under the curve (AUC) is a parameter that integrates both the duration and intensity of drug concentration (Pandey *et al*., 2020). The AUC is influenced by the rate of drug elimination from the body and the dosage administered (Baggot, 2001). There was no significant difference in the AUC ($p > 0.05$) between the group that received sulphadimidine alone and the group that was administered sulphadimidine and oxytetracycline concurrently. The AUC for sulphadimidine alone (1145.88 ± 5023.26 µg/ml·h) is comparable to that obtained in West African Dwarf (WAD) goats (1141.99 ± 90.51 µg/ml·h) (Agbo *et al*., 2024).

The elimination half-life is the duration required for fifty percent of a drug to be removed from the body. It is generally accepted that drugs are eliminated after approximately five half-lives. The half-life of the group administered sulphadimidine alone was significantly longer ($p < 0.05$; 8.02 ± 2.48 hours) compared to the group that received sulphadimidine in combination with oxytetracycline (7.94 ± 0.89 hours). The extended elimination half-life in the group receiving sulphadimidine alone corresponds with a significantly increased volume of distribution (Vd) (9.41 ± 2.07 l/kg) in the same group, compared to the Vd (9.02 ± 0.32 l/kg) in the group that received sulphadimidine and oxytetracycline concurrently. The T1/2β and Vd obtained in this study are consistent with findings from a study conducted on West African Dwarf (WAD) goats (Agbo *et al*., 2023).

V. Conclusion

The combination of sulphadimidine and oxytetracycline resulted in significant changes in the maximum absorption time (MAT), half-life (T1/2β), and volume of distribution (Vd) of sulphadimidine. Higher serum concentrations were maintained for a longer period following this combination. Therefore, it can be concluded that oxytetracycline exhibits a synergistic effect with sulphadimidine, and the combination of both drugs is recommended.

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