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Tylosin can alter the disposition kinetics of sulphadimidine in goats

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Abstract
The effect of Tylosin on the pharmacokinetics of sulphadimidine was evaluated using West African Dwarf (WAD) goats. In the experiment, eight (8) WAD goats comprising 4 males and 4 females, aged 1-2 years were used for the study. We administered sulphadimidine at a dose of 100 mg/kg body weight to goats in group A on the left gluteal muscle, while the goats in group B received sulphadimidine at a dose of 100 mg/kg on the right gluteal muscle and tylosin at a dose of 10 mg/kg on the left gluteal muscle. Blood samples were collected in all the experiments for a period of 48 h. Plasma samples obtained were analysed using spectrophotometer. Tylosin resulted in significant changes in the kinetics of sulphadimidine in WAD goats. The study concludes that sulphadimidine should be combined with tylosin in the treatment of bacterial diseases both of the gastrointestinal tract and the respiratory tract due to the synergistic interaction between the two drugs.

Keywords: Sulphadimidine, pharmacokinetics, tylosin, goats

1. Introduction
Sulphadimidine is one of the most widely used antibacterial agent in veterinary medicine, due to their low cost and relative efficacy in some bacterial and protozoan diseases (Agbo *et al.*, 2023) [1]. It is useful against gram positive and negative bacteria, toxoplasma and coccidia species (Barragry, 1994; Prescott, 2000) [2, 3]. The kinetics of sulphadimidine has been done in broilers (Onyeyili *et al.*, 2000) [4], dogs (Saganuwan *et al.*, 2003) [5], turkeys (Agbo *et al.*, 2016) [6] and goat (Agbo *et al.*, 2023, Akogwu *et al.*, 2017) [1, 7].
Sulphadimidine works by interfering with the synthesis of folic acid in bacteria. Folic acid is essential for bacteria to produce DNA and proteins necessary for their growth and survival. By blocking the enzymes involved in folic acid synthesis, sulphadimidine effectively inhibits the growth and multiplication of susceptible bacteria (Spoo and Reviere, 2001) [8].
Tylosin is a macrolide antibiotic with good activity against mycoplasma and gram positive organisms (Giguere, 2006) [9] and it is used in veterinary medicine to control respiratory diseases, mastitis, and dysentery in cattle and other farm animals (Kowalski *et al.*, 2002) [10].
Tylosin works by inhibiting bacterial protein synthesis. It binds to the bacterial ribosome, preventing the formation of functional proteins necessary for bacterial growth and reproduction (Gaynor and Mankin, 2005) [11].
There is little information on the effects of sulphadimidine on the pharmacokinetic of tylosin in goats. These studies will provide basis for recommending adjustments in dosage regimen and guide when co-administering sulphadimidine and tylosin.

2. Materials and Methods
2.1 Experimental animals
Eight (8) goats were obtained from local breeders in Wadata, Makurdi Local Government Area. They were housed in the goat pen at the Veterinary Teaching Hospital Joseph Sarwuan Tarka University Makurdi. The animals were stabilized for two weeks prior to experimentation. The animals were well fed and water was provided *ad libitum.* All the animals were handled according to ethical standards [12].

2.2 Reagents
1. Trichloroacetic acid (TCA) (Guangdong, China)
2. Sodium nitrite (Kermel, China)
3. Sulphamic acid (BDH Chemicals, England)
4. 8-OH quinoline (Sinopharm, China)
5. Sodium hydroxide (Qualikems, India)
6. Distilled water

2.3 Drugs
1. Sulphadimidine sodium (Shijiazhuang Guanghua Pharma. Co, Ltd. China)
2. Tylosin Tartrate (Shijiazhuang Guanghua Pharma. Co, Ltd. China)

2.4 Equipments
1. UV spectrophotometer
2. Vortex mixer
3. Test tubes and test tube rack
4. Measuring cylinder
5. Weighing scale
6. Spatula
7. EDTA tubes
8. Needle and syringes (2 ml)
9. Sample bottle containing EDTA
10. Centrifuge machine
11. Swabs
12. Cryo vials

2.5 Experimental design
Eight goats were used for the study. They were 1 year old and weighed approximately 13 to 13.5 kg. They were randomly separated into groups A and B consisting of 4 goats each. The goats in group A weighed 13.13±1.44 kg and goats in group B weighed 13.50±0.41 kg. Goats in group A received only sulphadimidine sodium on the left gluteal muscle at a dose of 100 mg/kg body weight. Goats in group B were given sulphadimidine sodium on the right gluteal muscle using 100 mg/kg as the dosage and tylosin was administered into the left gluteal muscle using 10 mg/kg as the dosage.

2.6 Blood sample collection
Basal blood sampling (2 ml) before medication was performed in each goat with further sampling at fixed times: 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, 24, 48 h after dosing of the drug preparation.
Blood samples were immediately centrifuged at 3,000 × g for 10 min, after which the plasma was recovered, identified, frozen and stored at -20 °C until analysed.

2.7 Determination of Sulphadimidine in Plasma
Plasma concentration of sulphadimidine was determined by a modified chemical assay method described by Nagaraja *et al.*, (2007) [13].

2.8 Pharmacokinetic analysis
The pharmacokinetic analysis of the plasma concentrations obtained was done by pharmacokinetic software 'PC Modfit V7.8'.

2.9 Statistical Analysis
Student's t-Test paired using Graph Pad Prism 5.03 for Windows at 5% level of significance.

3. Results
The mean plasma concentration of sulphadimidine in the goats administered sulphadimidine alone and sulphadimidine combined with tylosin is presented in table 1.
Sulphadimidine concentration of 79.36±5.41 µg/ml was obtained in the goats administered sulphadimidine alone while a concentration of 86.5±1.51 µg/ml was obtained in the goats administered sulphadimidine and tylosin concurrently at 0.25h. The plasma concentration of sulphadimidine increased until a peak concentration of 101.6±2.93 µg/ml and 87.08±1.30 µg/ml was reached at 1.5h in goat administered sulphadimidine alone and goats administered sulphadimidine and tylosin respectively.
The peak plasma concentration subsequently decreased and at 48h post administration, plasma concentration were 0.29±0.43 µg/ml and 0.73±0.51 µg/ml in goat administered sulphadimidine alone and goats administered sulphadimidine and tylosin respectively.
There was significant (p<0.05) differences in the plasma concentration of sulphadimidine between the two groups of goats at 1.5, 2 and 24 hours post sulphadimidine administration.

Table 1: Mean Plasma Concentrations of Sulphadimidine (µg/ml)

Time(h)	Sulphadimidine alone	Sulphadimidine/tylosin
0.25	79.36 ± 5.41	86.55 ± 0.48
0.5	93.28 ± 4.45	85.98 ± 1.51
1	98.19 ± 3.79	84.42 ± 1.56
1.5	101.60 ± 2.93	87.08 ± 1.30[a]
2	100.72 ± 2.75	86.90 ± 1.10[a]
4	79.42 ± 3.13	85.12 ± 1.40
6	55.51 ± 4.54	72.16 ± 2.5
8	37.83 ± 4.47	68.07 ± 2.01
10	27.70 ± 4.35	59.51 ± 1.76
12	16.59 ± 3.56	49.77 ± 2.21
24	4.40 ± 1.74	12.56 ± 0.74[a]
48	0.29 ± 0.43	0.73 ± 0.51

Data are presented as mean ± SEM; a = p<0.05, paired student's t Test, n = 4

The pharmacokinetic parameters of sulphadimidine in WAD goats administered sulphadimidine alone and those administered sulphadimidine and tylosin concurrently are shown in table 2.
Tylosin (10 mg/kg) significantly (p<0.05) increased all the pharmacokinetic parameters with exception of Tmax (h), β (1/h) and $T_{1/2\beta}$ (h).

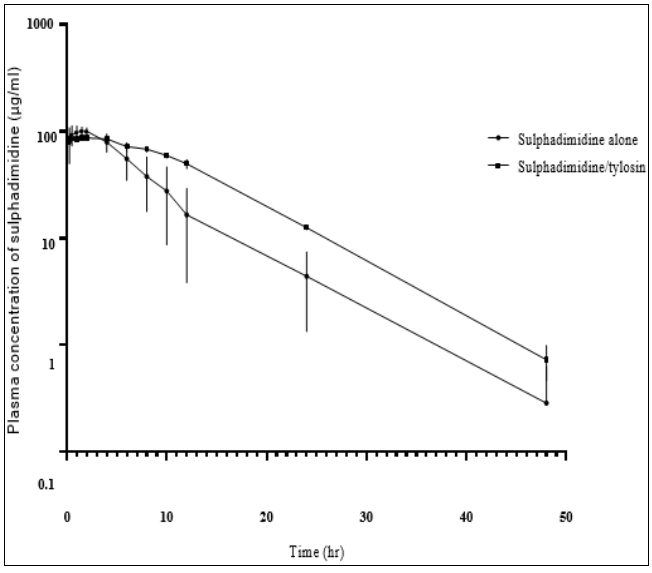

Fig 1: The mean semi-log plasma concentration of sulphadimidine

Table 2: Mean Pharmacokinetic Parameters of sulphadimidine

Parameters	Sulphadimidine alone	Sulphadimidine and tylosin
Tmax(h)	1.50	1.50
Cmax	105.80 ± 4.06	87.6 ± 0.37 [a]
MRT	6.90 ± 1.1	10.40 ± 0.17 [a]
α (1/h)	0.79 ± 0.24	0.2±0.02[a]
$T_{1/2\alpha}$ (h)	2.07 ± 0.93	3.46±0.02 [a]
MAT (h)	2.98 ± 1.35	4.50±0.02 [a]
β (1/h)	0.12± 0.02	0.11±0.00
$T_{1/2\beta}$(h)	6.0±0.12	5.90±0.14
Vd(L/kg)	13.9 ± 1.8	8.20 ± 0.4 [a]
Cl(L/kg/h)	1.60 ± 0.95	1.00 ± 0.02 [a]
AUC_{0-t}(µg/ml.h)	858.20 ± 158.35	1390.40 ± 27.89 [a]
$AUC_{0-\infty}$(µg/ml.h)	870.20 ± 156.30	1396.70 ± 27.45 [a]
$AUMC_{0-\infty}$ (µg/ml.h^2)	6492.70 ± 1901.84	14553.80 ± 342.89 [a]
$AUMC_{0-t}$(µg/ml.h)	6028.00 ±1930.82	14196.00 ± 638.73 [a]

Data are presented as mean ± SEM; a = $p<0.05$, paired student's t Test.

4. Discussion

The aim of this study was to investigate the effect of tylosin in the pharmacokinetic of sulphadimidine in West African dwarf goats. The combination is been used clinically in the management of Peste des Petits Ruminants (PPR) in goat mainly against secondary bacteria infection, protozoan infection of the gastrointestinal tract and respiratory tract.

Plasma concentration of sulphadimidine were observed for 48 hours (Table 1). Sulphadimidine combination with tylosin presented a two compartment open model (Fig 1). This is in agreement with the report of Agbo *et al.*, 2016 [6] in starved and non-starved domestic grower turkey, Akogwu *et al.*, 2017 [7] in WAD goats, Agbo *et al.*, 2019 [14], 2023 [5] in WAD goats.

These findings are at variance with report of Argaw and Brugere, 1990 [15] in sheep and goat, Onyeyili *et al.*, 1997 [16] in guinea fowl, domestic chicken and duck where sulphadimidine was eliminated by a single compartment model.

This could be due to specie or breed variation and differences in the site of administration.

The volume of distribution is the volume that would be required to contain the amount of drug present in the body at the same concentration as in the plasma or a factor that relates the amount of drug in the body to the concentration of drug in the plasma (Gustafson and Bradshaw pierce, 2011) [17]. This gives information on the drugs distribution in the body.

In the present study the group of WAD goats treated with sulphadimidine alone had a significantly ($p<0.05$) high volume of distribution of 13.9 ± 1.5 L/kg as against 8.20 ± 0.4 L/kg for the WAD goat treated with sulphadimidine and tylosin concurrently. This high volume of distribution in the group administered sulphadimidine alone is an indication of a more extensive penetration into the body fluids and tissue of the body. The volume of distribution may vary widely depending on the relative degree of its binding to plasma and tissue proteins. This indicated significant binding of sulphadimidine to plasma and tissue proteins when combined with tylosin.

The total body clearance reflects the elimination of the drug from the body (Agbo *et al.*, 2023) [1]. The higher the drug concentration in plasma the more the drug is presented for elimination. Therefore, clearance is the coefficient of proportionality between plasma drug concentration and elimination (Bourne, 2010) [18].

The total body clearance of sulphadimidine in the goats administered sulphadimidine alone was significantly (($p<0.05$) higher (1.60 ± 0.95 L/kg/h) as against that of the goats administered sulphadimidine and tylosin concurrently (1.00 ±0.02 L/kg/h). this suggest that less sulphadimidine is presented to the metabolic and excretory organs when combined with tylosin.

The Area under the concentration-time curve (AUC) is the integral of the plasma drug concentration time curve (Bourre, 2010) [18].

The AUC reflects the actual exposure of the drug after administration of a dose of the drug. It is dependent on the rate of elimination and the dose administered and inversely proportional to the drug clearance (Bourne, 2010) [18].

In the present study, the WAD goats treated with sulphadimidine combination with tylosin has a significantly ($p<0.05$) increased AUC (1390.40±27.89 µg/mL.h) compared to the WAD goats treated with sulphadimidine alone (854.20 ± 158.35 µg/mL.h). This indicates that the body exposure to the drug is longer in the goats treated with sulphadimidine and tylosin more than those treated with sulphadimidine alone. The longer body exposure to sulphadimidine in WAD goats treated with sulphadimidine and tylosin combination is possible because of the lower total body clearance and slower decline in the plasma drug concentration. This is also reflected in the MRT parameter, where the goats treated with sulphadimidine alone had a significantly ($p>0.05$) lower MRT (6.90±1.1 h) when compared to the goats treated with sulphadimidine and tylosin combination (10.40±0.17 h).

5. Conclusion

Sulphadimidine combination with tylosin has increased the plasma concentration of sulphadimidine for longer period of time. This implies synergistic interaction between the two drugs.

6. Conflict of Interest: None

7. Financial Support: None

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