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EFFECT OF DICLOFENAC ON THE PHARMACOKINETICS OF SULPHADIMIDINE IN WEST AFRICAN DWARF (WAD) GOATS FOLLOWING INTRAMUSCULAR ADMINISTRATION.

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ABSTRACT
Sulphadimidine an antimicrobial is widely used in veterinary medicine in the treatment of animal diseases. It can be combined with non-steroidal anti-inflammatory drugs to treat various systemic infections associated with fever, pain and other inflammatory conditions. This study was carried out to determine the effect of diclofenac on the pharmacokinetics of sulphadimidine in West African Dwarf goats. Eight (8) WAD goats of 1-2 years old with a mean weight of 17.73 $\pm$ 0.89 kg were separated into two groups of four animals consisting of two males and two female goats each. Sulphadimdine sodium (33.3%) was administered at a dose of 100 mg/kg body weight and diclofenac (2.5%) was administered at a dose of 2.5mg/kg body weight. Sulphadimidine was administered into the right gluteal muscle to goats in group 1. To the goats in group 2, sulphadimidine was administered into the right gluteal muscle and diclofenac into the left gluteal muscle concurrently. There was no significant difference ($p>0.05$) in pharmacokinetic parameters between the WAD goats treated with sulphadimidine alone and sulphadimidine co-administered with diclofenac. Based on the results obtained, it can be concluded that diclofenac can be safely and effectively combined with sulphadimidine to treat animal diseases associated with fever, pain and other inflammatory conditions.

KEYWORDS: Sulphadimidine, West African Dwarf goats, Diclofenac, Pharmacokinetics.

INTRODUCTION
Sulphadimidine has attained an active place in the armamentaria of antimicrobials used in veterinary medicine [1]. It is an extended spectrum antimicrobial useful in the treatment against gram positive and negative microorganisms, chlamydiosis, toxoplasmosis and coccidiosis.[2-3] Sulphadimidine is 79% bound to plasma proteins with a half-life of 3.88 to 15.4 h and has particularly large percentage (60-90%) excretion as acetylated derivatives.[4] The pharmacokinetics of sulphadimidine has been reported in various species of animals including bovine, caprine, ovine, porcine, and avian species.[4-10]

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medication for pain and inflammation. In addition to their anti-inflammatory effect, NSAIDs have antipyretic and analgesic properties.[11] Diclofenac is a non-steroidal anti-inflammatory drug which is widely used in human medical and veterinary practice[12] for the management of post traumatic pain, postoperative wound hyperalgesia, pain associated with movement and swelling, and for the relief of joint lameness in animals.[13-14] Diclofenac acts by the inhibition of the enzyme cyclo-oxygenase 1 and 2.[15]

Pharmacokinetic interactions between NSAIDs and antimicrobials have been reported by various workers.[16-21] Literature reviews have shown no studies on kinetic interactions between diclofenac and sulphadimidine in animals, particularly in goats. The present study was carried out to investigate the interaction of diclofenac with sulphadimidine and whether the use of diclofenac in conjunction with sulphadimidine may be advised or not.

MATERIALS AND METHODS
This study was carried out in the Department of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, Federal University of Agriculture, Makurdi. The West African Dwarf (WAD) goats were purchased from local breeders in Makurdi metropolis. The goats were stabilized for two weeks prior to experimentation. They were fed on pasture and concentrate and water was provided *ad libitum.*

All the animals were handled according to the international guiding principle for biomedical research involving animals [International Council for Laboratory Animal Science [ICLAS] and Council for International Organization of Medical Sciences (CIOMS)[22]], as approved by the College of Veterinary Medicine, Federal University of Agriculture, Makurdi, Ethical Committee.

Experimental design and drug administration

Eight (8) WAD goats of 1-2 years old with a mean weight of 17.73 ± 0.89 kg were separated into two groups of four animals consisting of two males and two female goats each. Sulphadimdine sodium (33.3%) (Shijiazhuang Guanghua Pharma. Co, ltd. China) was administered at a dose of 100 mg/kg body weight and diclofenac (2.5%) (Jiangsu Huayang Pharmaceutical Co., Ltd, China) was administered at a dose of 2.5 mg/kg body weight. Sulphadimidine was administered into the right gluteal muscle to goats in group 1. To the goats in group 2, sulphadimidine was administered into the right gluteal muscle and diclofenac into the left gluteal muscle concurrently.

Blood sample collection

Blood samples (2.0 ml) were collected through the left jugular vein of each goat prior to sulphadimidine administration and at these time periods post drug administration 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, 24, 48 h. The samples were collected using 23 G disposable needle and 2 ml syringe into heparinized tubes. The samples collected were centrifuged at 3000 rpm for 10 min and the plasma obtained and stored at -20°C until analysed.

Determination of sulphadimidine in plasma

Plasma concentration of sulphadimidine was determined by a modified chemical assay method described by Nagaraja *et al.* [23]. The method is based on the diazotization of sulphadimidine and coupling with 8-OH quinoline (Sinopharm, China) in alkaline media to yield red coloured products with absorption maxima at 500 nm. The procedure is briefly described below.

To 0.4 ml of plasma in a 5 ml glass test tube, 2 ml of distilled water was added, followed by 0.6 ml of 20% trichloroacetic acid (Guangdong, China). The resulting solution was mixed using a vortex mixer and centrifuged for 5 min. To the clear supernatant (2.5 ml), 0.15 ml of 1.0% sodium nitrite (Kermel, China) was added, mixed and allowed to stand for 5 min. There after 0.25 ml of 2.0% sulphamic acid (BDH Chemicals, England) was added, mixed and allowed to stand for 5 min. This was followed by addition of 0.2 ml of 0.5% 8-OH quinoline (Sinopharm, China). The resulting solution was mixed and allowed to stand for 5 min, followed by addition of 0.2 ml of 20% sodium hydroxide (Qualikems, India). The resulting solution was mixed and the absorbance read using a UV-spectrophotometer (spectrum lab 23A, 340- 1000 nm) at a wavelength of 500 nm.

The linear calibration curve of sulphadimidine in plasma within the range of 1.25-20.0 µg/ml was obtained by plotting absorbance on y-axis against time on x-axis. The calculation of the linear regression showed R^2=0.998.

The limit of detection (LOD) and limit of quantification (LOQ) of sulphadimidine in plasma were 0.08 and 0.24 µg/ml respectively. The intra-day and inter-day precision were 0.50 and 0.80 % respectively.

Calculation of pharmacokinetic parameters

The pharmacokinetic parameters for individual animals were calculated using established pharmacokinetic equations [24-26] and pharmacokinetic software (Kinetica 5.0, Thermo Fischer Scientific). Micro (α, β) constants were determined from all the plotted graphs obtained from the generated data.

Statistical analysis

The data on plasma kinetics and pharmacokinetic parameters were presented in graphical and tabular form respectively. Plasma concentrations and pharmacokinetic parameters were presented as Mean±Standard Error of Mean (SEM) and analyzed by Student's t test paired using Graph Pad Prism 6.03 for windows at 5% level of significance.

RESULTS

The data for sulphadimidine in groups treated with sulphadimidine alone and sulphadimidine co-administered with diclofenac best fit a two compartment open model (Figure 1).

The pharmacokinetic parameters of WAD goats administered sulphadimidine alone and those given sulphadimidine in combination with dicofenac are shown in table 1. There was no significant difference ($p>0.05$) in pharmacokinetic parameters between the WAD goats treated with sulphadimidine alone and sulphadimidine co-administered with diclofenac.

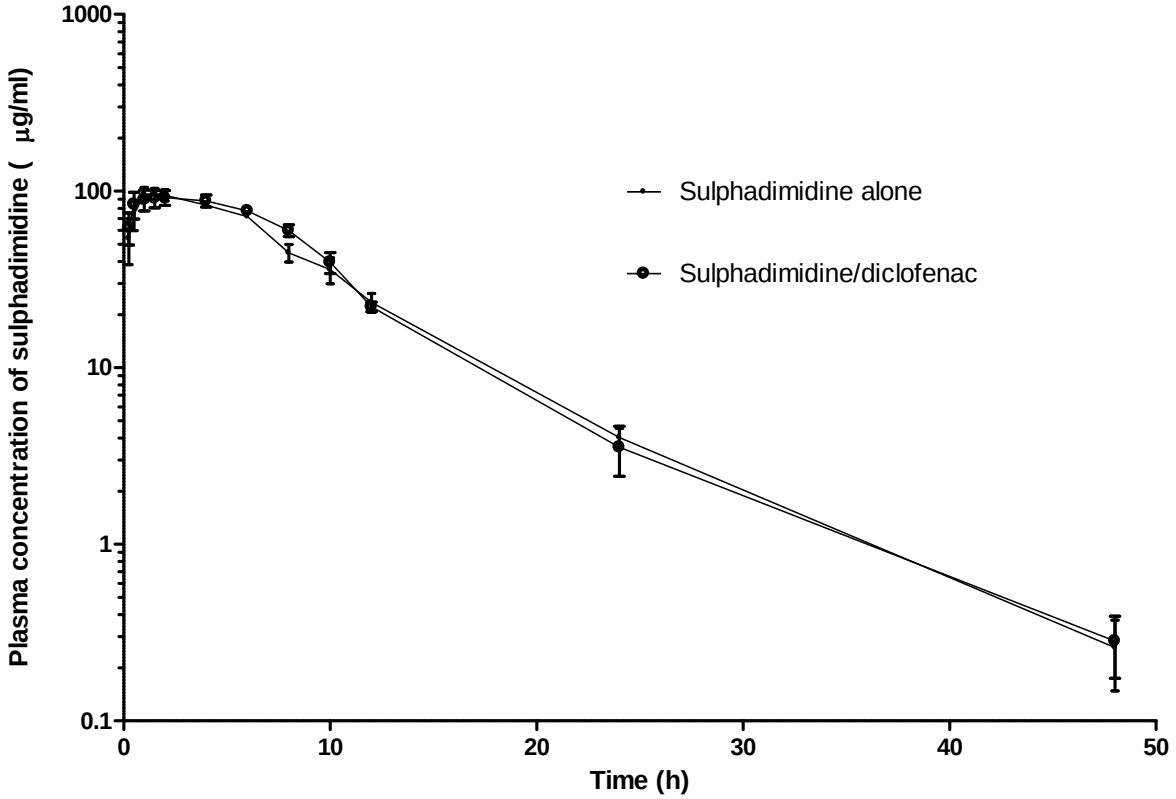

Fig 1: Mean and SEM plasma concentration-time profile of sulphadimidine in WAD goats following intramuscular treatment with sulphadimidine (100 mg/kg) alone and sulphadimidine (100 mg/kg) co-administered with diclofenac (2.5 mg/kg) (n=4).

Table 1: Pharmacokinetic parameters of sulphadimidine in WAD goats following intramuscular treatment with sulphadimidine (100 mg/kg) alone and sulphadimidine (100 mg/kg) co-administered with diclofenac (2.5 mg/kg) (n=4).

Kinetic parameters	Sulphadimidine alone	Sulphadimidine/ diclofenac
Cmax(µg/ml)	99.08±6.41	94.81±8.43
Tmax(h)	1.50±0.20	2.00±0.73
α (1/h)	1.60±0.50	1.30±0.22
$T_{1/2\alpha}$ (h)	0.59±0.18	0.58±0.10
MAT (h)	0.86±0.26	0.84±0.14
β (1/h)	0.13±0.01	0.15±0.05
$T_{1/2\beta}$ (h)	5.33±0.55	5.15±0.96
Vd(L/kg)	15.01±2.99	12.81±1.08
Cl(L/kg/h)	1.88±0.22	1.86±0.34
MRT(h)	7.47±0.45	7.29±0.39
AUC_{0-t}(µg/ml.h)	957.16±60.71	1000.73±97.36
$AUC_{0-\infty}$(µg/ml.h)	962.89±59.85	1003.14±98.12
AUMC(µg/ml.h^2)	7618.94±449.81	7388.94±976.53

Data are presented as mean±SEM; p>0.05, paired student's t test

Cmax, maximum concentration; Tmax, time of maximum concentration; α, absorption rate constant; $T_{1/2\alpha}$, absorption half life; β, elimination rate constant; $T_{1/2\beta}$, elimination half life; Vd, volume of distribution; Cl, total body clearance; MRT, mean residence time; AUC_{0-t}, area under the plasma concentration vs time curve from 0 to time; $AUC_{0-\infty}$, area under the plasma concentration vs time curve from 0 to infinite; AUMC, Area under the moment curve.

DISCUSSION

The results of the present study, showed that intramuscular sulphadimidine administration alone or its combination with diclofenac to the WAD goats resulted in measurable blood levels of sulphadimidine for 48 h. Sulphadimidine was eliminated in a biphasic process when administered intramuscular alone or concurrently with diclofenac. This finding disagrees with that of

Onyeyili *et al.*[10] in guinea fowls, domestic chicken and ducks. The differences in the route of administration and the specie of animal used may account for the differences noticed. However, the findings in this present study agrees with those of other workers including Nawaz[27] and Saganuwan *et al.*[1] in dogs, Onyeyili *et al.*[28] in broiler chickens, Nielson and Rasmussen[29] in cow, Atef *et al.*[30] in buffaloes and Agbo *et al.*[9] in starved and non starved domestic grower turkeys. Kinetic profiles of drugs a time are known to differ from one animal to another even within the same specie of animal.[31]

The pharmacokinetic parameters of sulphadimidine was not significantly different between the WAD goats administered sulphadimidine alone and those administered sulphadimidine and diclofenac concurrently (table 1). This may be due to the rapid absorption and elimination of diclofenac from goat. Dicofenac administered with enrofloxacin resulted in significant differences in the pharmacokinetic parameters of enrofloxacin.[18] This was attributed to the direct inhibition of cytochrome P_{450} by enrofloxacin.

The elimination half lives of sulphadimidine in the WAD goats administered sulphadimidine and diclofenac concurrently was similar to that reported in sheep (4.72 h)[7] and shorter than that reported in cattle (9.46 $\pm$0.93 h, 8.32 $\pm$0.96 h)[32], goat (7.24 $\pm$1.05 h)[4] and sheep (9.51 h).[33] This may be due to differences in specie, route of administration and analytical technique employed.

CONCLUSION

The results from the study showed that diclofenac can be used safely and effectively along with sulphadimidine in the treatment of diseases caused by microorganisms that are sensitive to sulphadimidine and also associated with fever, pain and other inflammatory conditions.

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