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## The Effect of Sulphamethazine Combination on the Plasma Kinetics of Chloramphenicol in Sokoto Red Goats

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**Abstract:** A comparative pharmacokinetic study of chloramphenicol (25 mg kg<sup>-1</sup> intravenous) by chemical assay method and its combination with sulphamethazine (33 mg kg<sup>-1</sup>) in Sokoto red goats has revealed that the mean peak plasma concentrations at 0.08 h post drug administration were not significantly different. However, various pharmacokinetic parameters were significantly altered ( $p < 0.05$ ) after the combination therapy; the total body clearance (Cl) and elimination constant ( $\beta$ ) were significantly higher whereas the half life of elimination ( $t_{1/2} \beta$ ) and the distribution rate constant were significantly lower. These changes observed in this study could be an indication that, the combination therapy may require a reduced chloramphenicol dose without necessarily minimising the efficiency of the drug and this may also possibly reduce the risk of dose-related toxicity.

**Key words:** Chloramphenicol, pharmacokinetic, sulphamethazine, concentration, plasma

### INTRODUCTION

Chloramphenicol and Sulphamethazine are two antibiotics frequently used in the treatment of both animals and human diseases in this environment. Occasionally these agents are deliberately or accidentally combined. The effect of such combination has never been reported. Antagonism or potentiation of the effects of one drug by another after a combined administration of the drugs is a well known phenomenon. More recently, it has been reported that in some cases the interactions have a pharmacokinetic rather than pharmacodynamic basis (Gibaldi, 1977). The absorption, distribution, excretion or metabolism of a drug may be markedly affected by the concomitant administration of a second drug, leading to differences in the plasma drug concentrations produced by a given dose and therefore, to differences in the dose-response relationship (Hussar, 1975). In the present experiment, this phenomenon will be studied by combining chloramphenicol and sulphamethazine in healthy goats. Chloramphenicol and sulphonamide are frequently used together in undifferentiated febrile illness in both humans and animals. These can be demonstrated in the combined prescription of anti-malarial drugs such as pyrimethamine + sulphadoxine (Fansidar) and chloramphenicol to treat undifferentiated febrile illness (malaria/typhoid fever); trimethoprim+sulphadimidine (cotrimoxazole) and chloramphenicol in intractable cases

of *Salmonella* infection in humans, also the combination of the two drugs to treat multiple infections in animals. The objective of the present study was to compare the kinetic profile of chloramphenicol and its combination with sulphamethazine in healthy red Sokoto goats following a single intravenous administration.

### MATERIALS AND METHODS

**Animals and treatment:** Five adult goats of both sexes (14 to 20 kg) were used. The goats were clinically healthy at the beginning of the experiment. They were kept in goat pens at the Faculty of Veterinary Medicine, Usmanu Danfodiyo University, Sokoto and fed hay and concentrate. Water was provided *ad libitum*. The same goats were used for both aspects of the study with an interval of one month between chloramphenicol alone and the drug with its combination with sulphamethazine. The goats were dosed intravenously with chloramphenicol (25 mg kg<sup>-1</sup>) and blood samples were collected from the animals at predetermined periods [0.08, 0.25, 0.5, 1.0, 2.0, 3.0, 6.0, 9.0, 12.0, 24.0, 48.0 and 72.0 post drug administration] h. Chloramphenicol was administered into the left jugular vein and blood collected from the right jugular vein. Control samples of blood were collected 15 min prior to injection of chloramphenicol.

All blood samples were collected in vials containing Sodium EDTA as anticoagulant. The samples were

centrifuged immediately on collection at 1500 rpm for 15 min to obtain the plasma which was stored in a freezer at -20°C until analysed.

Twenty-five milligram per kilogram (25 mg kg<sup>-1</sup>) of chloramphenicol and thirty-three milligram per kilogram (33 mg kg<sup>-1</sup>) of sulphamethazine were administered intravenously through the left jugular vein to the goats, during the combination study and the blood samples were collected from the contralateral vein. The samples were similarly processed and stored pending the analyses for chloramphenicol.

**Chloramphenicol determination from plasma:**

Chloramphenicol was extracted from all plasma samples chemically using a colorimetric method (Kakemi *et al.*, 1962; Hughes and Diamond, 1964; Watson, 1979). Briefly, Trichloroacetic acid was used to coagulate plasma proteins from the blood samples. The supernatant obtained was treated with phosphate buffer, amylicetate, sodium hydroxide and isonicotinic acid. The density of the resultant colour change was measured with a Spectrophotometer [SP-6 Visible Pye Unicam, England] at 430 nanometer.

**Calculation of pharmacokinetic constants:**

Pharmacokinetic analysis (Baggot, 1980) was performed by standard procedure employing a preprogrammed software (instat) for non-linear regression analysis. The two compartment pharmacokinetic model was confirmed using a log-linear plot of drug concentration in plasma against time and least squares analysis linear regression.

Tests for the significance of difference between the mean parameters in respect of chloramphenicol alone and its combination with sulphamethazine in the treated goats were performed using student's t-test for paired comparisons.

**RESULTS**

The results presented in this study following intravenous administration of chloramphenicol alone as a reference indicated that sulphamethazine (33 mg kg<sup>-1</sup>) administration intravenously in combination with chloramphenicol (25 mg kg<sup>-1</sup>) to goats significantly altered some kinetic profiles of chloramphenicol.

Data presented in Fig. 1 and 2 indicate that there was no significant change in the peak plasma level of chloramphenicol (26.62±2.26 and 26.26±1.34 µg mL<sup>-1</sup>) measured when chloramphenicol was administered alone and in combination with sulphamethazine, respectively. These peak plasma concentrations were recorded at 0.08 h after the drug administration. The peak plasma concentrations were followed by gradual decline in the

Table 1: Pharmacokinetic parameters for chloramphenicol in healthy goats given chloramphenicol (25 mg kg<sup>-1</sup>) and its combination with sulphamethazine intravenously

Parameters	Chloramphenicol alone (n = 5) <sup>a</sup>	Chloramphenicol plus sulphamethazine (n = 5) <sup>a</sup>
A (mg mL <sup>-1</sup> )	24.00±2.55	28.00±2.86 <sup>b</sup>
B (mg mL <sup>-1</sup> )	7.00±0.64	6.20±0.42
C <sub>∞</sub> (mg mL <sup>-1</sup> )	31.00±1.01	34.20±3.48
AUC (h mg mL <sup>-1</sup> )	32.81±0.76	21.54±1.22 <sup>b</sup>
CL (L/kg/h)	0.76±0.21	1.16±0.18 <sup>b</sup>
V <sub>dβ</sub> (L kg <sup>-1</sup> )	3.13±0.51	3.24±0.29
t <sub>1/2β</sub> (h)	2.98±0.21	1.95±0.14 <sup>b</sup>
t <sub>1/2α</sub> (h)	0.095±0.02	0.106±0.05
K <sub>21</sub> (h <sup>-1</sup> )	1.82±0.23	1.49±0.21 <sup>b</sup>
K <sub>12</sub> (h <sup>-1</sup> )	4.55±0.44	3.90±0.32 <sup>b</sup>
K <sub>el</sub> (h <sup>-1</sup> )	1.19±0.28	1.59±0.24 <sup>b</sup>
α (h <sup>-1</sup> )	7.28±0.52	6.63±0.48
β (h <sup>-1</sup> )	0.24±0.06	0.36±0.04 <sup>b</sup>
Vc (L kg <sup>-1</sup> )	0.762±0.002	0.731±0.04

a: Data represents mean±SD, b: Data for goats following combination treatment significantly different from those with chloramphenicol alone (p<0.05, using student's t-test).

drug plasma levels until minimum detectable levels (0.34±0.09 and 0.18±0.14 µg mL<sup>-1</sup>) were recorded, respectively at 6 h and 9 h in the goats given chloramphenicol alone and chloramphenicol plus sulphamethazine.

Semilogarithmic plot of the data shown in Fig. 1 (chloramphenicol alone) and Fig. 2 (chloramphenicol and its combination with sulphamethazine) indicate that, the data should best fit a two compartment open model. The character of the biexponential curve could be described by the equation:

$$Cp^t = 24.0e^{-7.28t} + 7.0e^{-0.24t} \text{ (in goats treated with chloramphenicol alone) and}$$

$$Cp^t = 28.0e^{-6.63t} + 6.20e^{-0.36t} \text{ (in goats given the drug combination)}$$

where, Cp<sup>t</sup> is the concentration in plasma (µg mL<sup>-1</sup>) and (t) is the time (h).

The volume of distribution (V<sub>dβ</sub>±SD = 3.13±0.51 L kg<sup>-1</sup>) in goats administered chloramphenicol alone was not significantly different from the volume of distribution (V<sub>dβ</sub>±SD = 3.24±0.29 L kg<sup>-1</sup>) in goats given combination treatment. It was observed that combination of chloramphenicol with sulphamethazine in goats significantly increased the total body clearance (Cl) (1.16±0.18 vs. 0.76±0.21 L/kg/h) and elimination rate (β) (0.36±0.04 vs. 0.24±0.06 h<sup>-1</sup>). It also decreased elimination half-life (t<sub>1/2β</sub>) (1.95±0.14 vs. 2.98±0.21 h), area under the curve (AUC) (21.54±1.22 vs. 32.81±0.076 h µg mL<sup>-1</sup>) and distribution rate constant (α) (6.63±0.48 vs. 7.28±0.52 h<sup>-1</sup>) (Table 1).

**DISCUSSION**

The results of the present pharmacokinetic study show that the peak concentrations attained in goats given

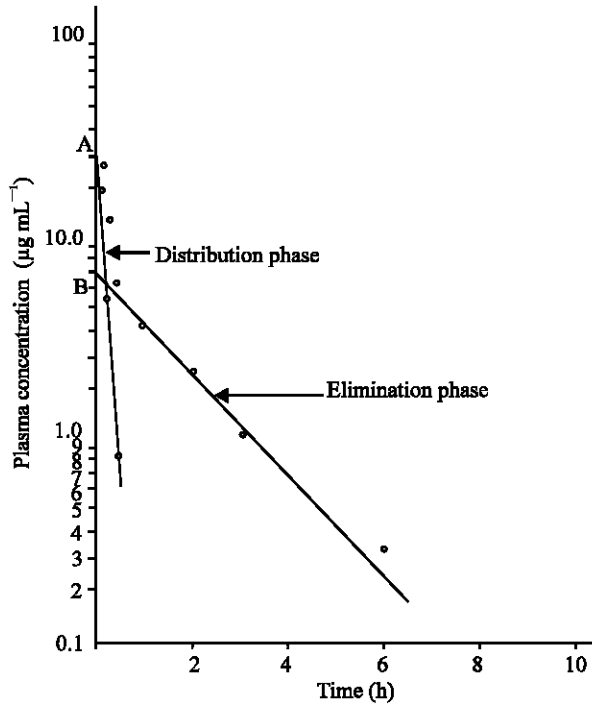


Fig. 1: Semilogarithmic plot of chloramphenicol disappearance in plasma versus time after intravenous administration of a single dose of chloramphenicol ( $25 \text{ mg kg}^{-1}$ ) in healthy goats

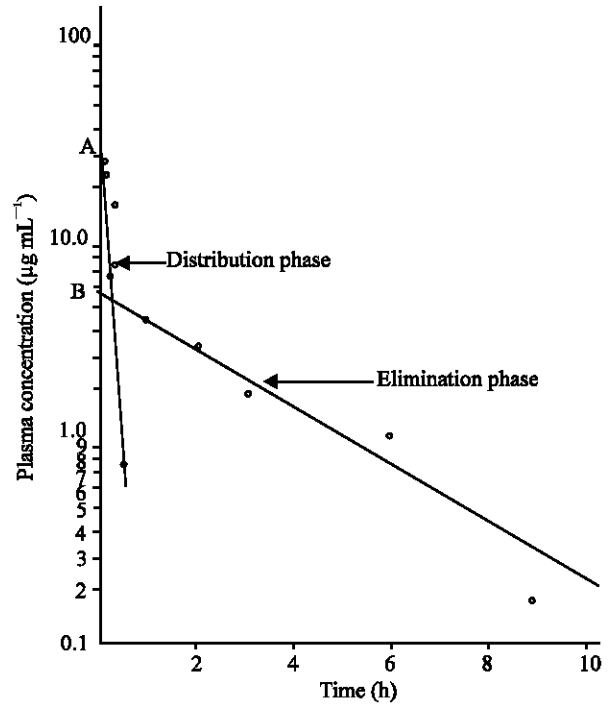


Fig. 2: Semilogarithmic plot of chloramphenicol disappearance in plasma versus time after intravenous administration of a single dose of chloramphenicol ( $25 \text{ mg kg}^{-1}$ ) combined with sulphamethazine to healthy goats

chloramphenicol alone and its combination with sulphamethazine were lower than those obtained in other species of animals (Burrows *et al.*, 1986; Anadon *et al.*, 1994). However, the peak concentrations obtained in this study were higher than that obtained by Watson (1979) in healthy dogs. The disposition of chloramphenicol after intravenous administration and its combination with sulphamethazine could be described by two compartment model. Experiments performed by other workers have led to the same conclusion (Watson, 1979; Burrows *et al.*, 1986; Anadon *et al.*, 1994; Mercer *et al.*, 1978; Sanders *et al.*, 1988).

The disappearance of the drug from the plasma of goats was characterised by an initial rapid distribution phase followed by a slower elimination phase. Chloramphenicol distributed very rapidly and widely in the body as evidenced by a high distribution rate constant ( $\alpha$ ), small distribution half-life ( $t_{1/2\alpha}$ ) values and the large volume of distribution [ $V_d^d$ ].

There were marked alterations in pharmacokinetics parameters in goats treated with chloramphenicol and sulphamethazine combination when compared with the animals given chloramphenicol alone (Table 1).

The apparent volume of distribution for chloramphenicol in goats treated with chloramphenicol alone ( $3.13 \pm 0.51 \text{ L kg}^{-1}$ ) and its combination with sulphamethazine ( $3.34 \pm 0.29 \text{ L kg}^{-1}$ ) observed in the

present study indicated considerable tissue penetration of the antibiotic either when administered alone or in combination with sulphamethazine. Chloramphenicol is known to be widely distributed to organs and tissues of the body (Anadon *et al.*, 1994).

The possible explanations to increased total body clearance and elimination rate constant in the goats treated with a combination of chloramphenicol and sulphamethazine when compared to the goats treated with chloramphenicol alone may be due to decreased plasma protein binding of chloramphenicol. Binding of drug to plasma proteins restricts its distribution, thereby limiting its biophasic availability and can influence elimination of the drug from the body. The presence of sulphamethazine may have restricted the binding of chloramphenicol to plasma albumin, hence increasing its elimination through the process of metabolism and excretion (Laurence *et al.*, 1997). Sulphaphenazone has been reported to displace a significant amount of warfarin from albumin (Sellers and Koch-Weser, 1970). This displacement temporarily elevates plasma levels of unbound warfarin and thereby increases the hypothermic effect by 40-50% (Sellers and Koch-Weser, 1970). Displacement of chloramphenicol from binding sites on plasma proteins could also account for the decreased elimination half-life for chloramphenicol

in goats treated with both chloramphenicol and sulphamethazine compared to goats given chloramphenicol alone. It is a fact that any physiologic state or condition that decreases the plasma protein binding of drugs increases the access of the drug to its sites of elimination (Laurence *et al.*, 1997).

Drugs interaction observed may also result from activities during renal excretion. Interaction at this level may result from the competition between drugs sharing the same carrier protein (Triggs *et al.*, 1975). This study has shown that, a combination therapy between chloramphenicol and sulphamethazine may increase the concentration of free chloramphenicol and also promote the rapid removal of the drug from the body. This could be an indication that the combination therapy may require a reduced chloramphenicol dose without necessarily minimising the efficacy of the drug and this may also possibly reduce the risk of dose related toxicity. It has been reported that, poor renal function in neonates and other states of renal insufficiency do result in increased plasma concentration of the drug and increased risk of toxicity (Slaughter *et al.*, 1980).

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