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Pharmacokinetics of Chloramphenicol Following Intravenous and Intramuscular Administration of the Drug to Healthy Sokoto Red Goats

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Abstract: Pharmacokinetics studies were performed in healthy red Sokoto goats using chloramphenicol 25 mg kg⁻¹. Following the drug administration intravenously and intramuscularly samples of plasma were obtained in the goats at various time intervals. Measurable blood levels of the drug were obtained in goats for 6 h after intravenous injection and for 9 h after intramuscular administration. A mean plasma concentration of chloramphenicol (25.63±2.01 µg mL⁻¹) was obtained at 0.08 h (5 min) after the intravenous administration of the drug while the peak plasma concentration of the drug following intramuscular treatment was 9.64±0.74 µg mL⁻¹ after 0.25 h (30 min). The apparent volume of distribution and the total body clearance of chloramphenicol from the Sokoto red goats were higher after intramuscular than intravenous administration. About 80% of the drug administered intramuscularly reached the plasma. This result has yielded baseline data for further investigation(s) of the drug.

Key words: Chloramphenicol, goat, concentration, plasma, pharmacokinetics

INTRODUCTION

Over the years since its discovery in 1947, chloramphenicol has continued to generate a lot of interests and controversies among scientists the world over, hence a significant amount of studies has been done and reported on the drug^[1-3].

It has been successfully used in the treatment of diseases like typhoid fever, bacterial cystitis, conjunctivitis, haemorrhagic septicaemia, infectious diarrhoea, salmonellosis, otitis media etc.^[4,5]. Chloramphenicol is still the drug of choice in the treatment of typhoid enteritis in humans especially in third world countries and the degree of resistance developed toward this antibiotic by microbes is still very minimal. In Nigeria, there has been of recent a phenomenal increase in the use of chloramphenicol, which does not correspond with a rising incidence of chloramphenicol sensitive infections. There is this unveiling scenario whereby patients with febrile illness "malaria" who do not respond to chloroquine are presumptively considered to have typhoid fever and thereby treated with chloramphenicol. This is so because, widal test the easily performed diagnostic test for this disease is very unreliable and cephalosporines, the alternative drug is very expensive^[6]. Chloramphenicol has been grossly abused by both medical workers and the patients who indiscriminately take the drug on their own.

The high success rate of chloramphenicol in treating several life threatening gram negative bacterial infections; its relative cheapness in terms of cost which makes it affordable and the low level of resistance to its activity has stimulated interest among investigators for further research to find additional and better uses of the drug or minimize its toxic effects such as bone marrow depression, blood dyscrasia and grey baby syndrome associated with its use.

Ironically, despite the widespread use of chloramphenicol in the tropics, few or no relative data are available on its kinetics. In view of this, it seems more logical to generate information about chloramphenicol use in animals.

Previous studies of the kinetics of chloramphenicol have been carried out in several species of animals^[3,7-9]. However, we are not aware of any in goats especially the red Sokoto breed indigenous to north western Nigeria. Most of the previous studies were conducted outside this environment and according to Nilsson *et al.*^[10], in order to use a drug effectively, it is important to investigate the detailed pharmacokinetics of the drug in a particular specie and environment in which the drug is to be used clinically. The pharmacokinetic study of chloramphenicol in the red Sokoto goats is undertaken in order to generate information on the drug and further provide a baseline data for comparison with subsequent studies.

MATERIALS AND METHODS

Animals treatment: Five healthy adult red Sokoto goats of both sexes weighing 12 to 20 kg were used for the study. The animals were purchased from Sokoto Cattle Market and were housed in pens at the Faculty of Veterinary Medicine, Usmanu Danfodiyo University, Sokoto. They were fed with hay and concentrate. Water was provided *ad libitum*.

Each goat was physically examined and blood samples collected for hematocrit, red blood cells count, differential leukocytes count, blood urea nitrogen and serum alanine amino transaminase determination. They were dewormed two weeks before the start of the study. The same goats were used for both intravenous and intramuscular studies with an interval of one month between the studies. These goats were dosed intravenously with chloramphenicol at 25 mg kg⁻¹ body weight through the left jugular vein and blood samples were collected from the contralateral vein. During the intramuscular study, chloramphenicol was administered to the goats in the left gluteal muscle and blood samples obtained from the right jugular vein. After the intravenous study, the animals were rested for one month and physically re-examined and blood chemistries and complete blood counts determined before they were used again for the intramuscular study.

Sample collection: Fifteen minutes before the administration of the drug, control samples of blood were collected from the goats. Following drug administration, blood samples were collected at 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 h. The blood samples were put into 10 mL tubes containing Disodium ethylenediamine tetra-acetate (EDTA) as anticoagulant. The blood samples were centrifuged immediately after collection at 1,500 rpm. for 15 min using a centrifuge (Uniscope, SM800B, Surgfriend Med. England). All plasma samples were stored at -20°C until they were analysed for presence of chloramphenicol.

Chloramphenicol determination from plasma: Total chloramphenicol was determined using the method of Kakemi *et al.*^[11] as modified by Hughes and Diamond^[12] and Watson^[13].

The interference with the chloramphenicol assay which can result from a high blood bilirubin level^[14] was investigated for plasma samples obtained at the following periods: pre-, peak- and post-concentration samples, following chloramphenicol administration intravenously and intramuscularly. These samples were analysed with and without charcoal. The effect of bilirubin interference is therefore included in the results.

Pharmacokinetic analysis: Pharmacokinetic analysis of the experimental data obtained from the plasma was performed for each goat using standard procedures^[15]. A pre-programmed desk calculator with a programme for non-linear regression analysis was used. The pharmacokinetic parameters and constants were determined using methods previously described^[16]. The following pharmacokinetic parameters were calculated: the half-life ($t_{1/2}$), concentration at zero time (C_p^0), distribution rate constant (α), elimination rate constant (β), zero-time intercepts (A and B), absorption rate constant (γ), volume of distribution ($V^d\beta$), total body clearance (CL), area under the curve (AUC), time maximum (t_{max}), concentration maximum (c_{max}) and bioavailability (F).

The results were expressed as mean±SD. Tests for significance between mean parameters in respect of intravenously and intramuscularly treated goats were performed, using the student's 't'-test and the "null" hypothesis was rejected at 5% level of probability^[17].

RESULTS

The result presented in this study using intravenous route of administration as a reference indicates that chloramphenicol administered intramuscularly to goats at 25 mg kg⁻¹ body weight was readily absorbed. The intravenous and intramuscular injection of chloramphenicol to goats resulted in a measurable blood levels for 6 and 9 h, respectively. A mean peak plasma concentration of 25.63±2.01 µg mL⁻¹ of chloramphenicol was achieved at 0.08 h (5 min) after intravenous drug administration (Fig. 1). This was followed by a constant decrease in plasma chloramphenicol concentration. Five min (0.08 h) after intramuscular chloramphenicol injection, the plasma concentration was observed to be 5.60±0.56 µg mL⁻¹. An increase in plasma concentration was observed until a peak chloramphenicol concentration was recorded at 0.50 h (30 min) after drug administration. This was followed by a decrease in plasma chloramphenicol concentrations to 0.34±0.08 mg kg⁻¹ after 9 h (Fig. 2). No detectable level of drug was measured in plasma after 9 h.

The disposition kinetics of chloramphenicol in red Sokoto goats, following a single dose of the drug at 25 mg kg⁻¹ body weight intravenously and intramuscularly are shown in Table 1. The pharmacokinetic evaluation of the drug administered intravenously indicated that the data should fit a two-compartment model (Fig. 1). In the example as shown in Table 1, the character of the bi-exponential curve might best be described by:

$$C_p^t = 30.0 e^{-6.74t} + 6.5 e^{-0.35t}$$

where, C_p^t is the concentration in plasma (µg mL⁻¹) and (t) is the time (h). According to the plot (Fig. 1), the initial

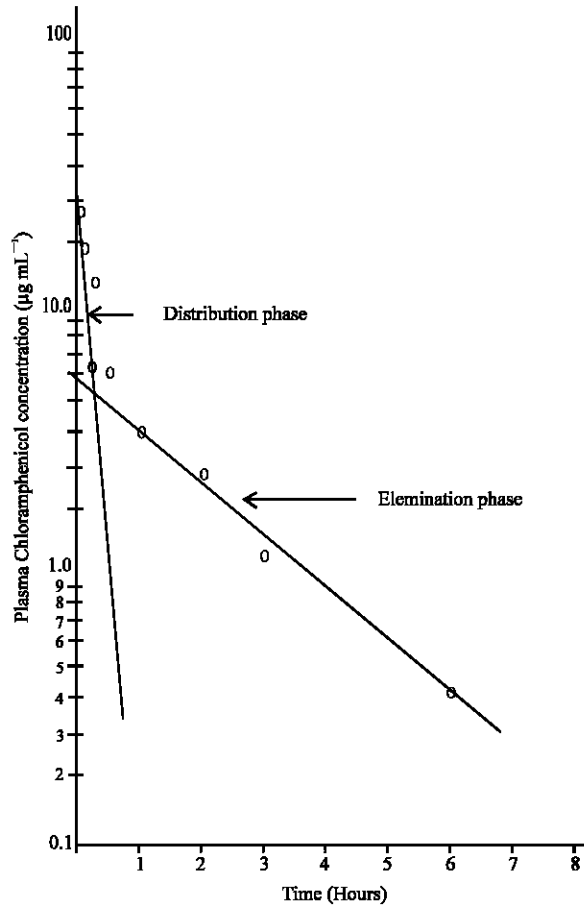


Fig. 1: Semilogarithmic plot of chloramphenicol disappearance in plasma versus time after administration of a single dose of chloramphenicol (25 mg kg^{-1}) intravenously to healthy goats

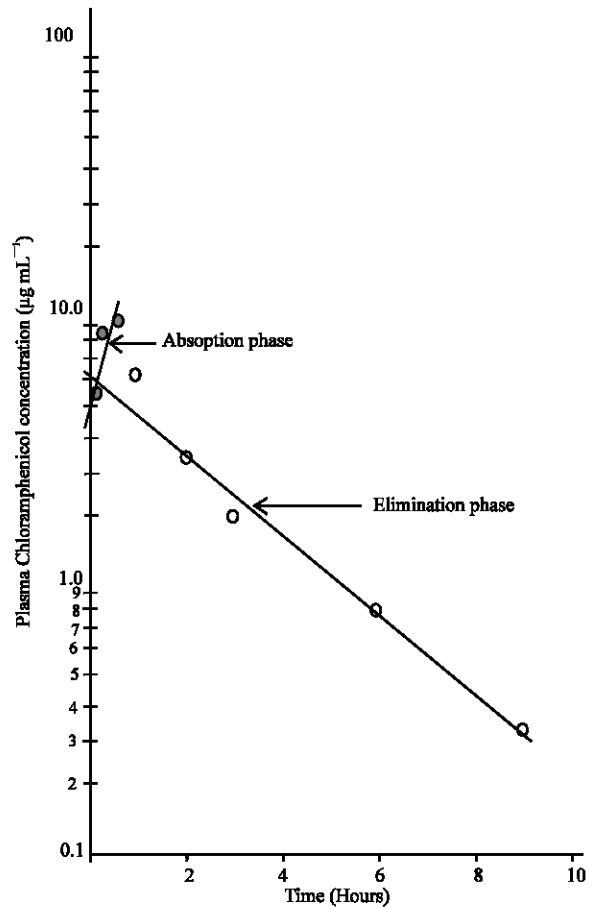


Fig. 2: Semilogarithmic plot of chloramphenicol disappearance in plasma versus time after administration of a single dose of chloramphenicol (25 mg kg^{-1}) intramuscularly to healthy goats

Table 1: Disposition kinetics of chloramphenicol after intravenous and intramuscular administration in healthy goats

Kinetic Parameters	Intravenous (n = 5) ^a	Intramuscular (n = 5) ^b
A ($\mu\text{g mL}^{-1}$)	30.0±16.51	-
B ($\mu\text{g mL}^{-1}$)	6.5±1.18	6.4±0.38
C_p ($\mu\text{g mL}^{-1}$)	36.5±5.21	-
AUC ($\text{h } \mu\text{g mL}^{-1}$)	23.02±2.46	11.16±2.04 ^b
CL ($\text{L kg}^{-1} \text{ h}^{-1}$)	1.09±0.21	2.24±0.71 ^b
V_d (L kg^{-1})	3.10±0.41	3.85±0.46 ^b
$T_{1/2}(\beta)$ (h)	1.97±1.23	1.19±0.07 ^b
$T_{1/2}(\alpha)$ (h)	0.105±0.02	-
$T_{1/2}(\gamma)$ (h)	-	0.076±0.01
α (h^{-1})	6.74±1.11	-
β (h^{-1})	0.35±0.18	0.58±0.03 ^b
γ (h^{-1})	-	9.16±1.63
K_{21} (h^{-1})	0.149±0.28	-
K_{12} (h^{-1})	1.58±0.31	-
K_{10} (h^{-1})	4.08±0.52	-
Vc (L kg^{-1})	0.68±0.05	-
t_{max} (h)	-	0.50
C_{max} ($\mu\text{g mL}^{-1}$)	-	9.64±0.74
F (%)	-	80.39±4.21

a) Data represents mean±SD, b) Data for intramuscular injection significantly different from those of intravenous injection at $p < 0.05$ using students t-test

concentration (C_p) was calculated to be $36.5 \pm 5.21 \mu\text{g mL}^{-1}$, with a distribution rate constant and half-life of $6.74 \pm 1.11 \text{ h}^{-1}$ and $0.105 \pm 0.02 \text{ h}$ in intravenously dosed goats respectively. The elimination rate constant was $0.35 \pm 0.18 \text{ h}^{-1}$, with an elimination half-life of $2.45 \pm 1.23 \text{ h}$. The apparent volume of distribution was calculated to be $3.10 \pm 0.41 \text{ L kg}^{-1}$. For the intramuscularly dosed animals, the absorption rate constant (γ) was calculated to be $9.16 \pm 1.63 \text{ h}^{-1}$, with absorption half-life of $0.076 \pm 0.01 \text{ h}$. The elimination rate constant was found to be $0.58 \pm 0.03 \text{ h}^{-1}$ with an elimination half-life of $1.19 \pm 0.07 \text{ h}$. The volume of distribution was calculated to be $3.85 \pm 0.46 \text{ L kg}^{-1}$. Administration of the drug intramuscularly resulted in a significantly ($p < 0.05$) increased total body clearance (Cl), volume of distribution (V_d) and elimination rate constant (β) and a decreased elimination half-life ($t_{1/2}\beta$) when compared to the data obtained from goats treated intravenously. The bioavailability of chloramphenicol after intramuscular administration was calculated as $80.39 \pm 4.21\%$.

DISCUSSION

A mean plasma concentration of $9.64 \pm 0.74 \mu\text{g mL}^{-1}$ of chloramphenicol was attained within 30 min (0.5 h) (peak concentration) after intramuscular injection and $25.63 \pm 2.01 \mu\text{g mL}^{-1}$ within 5 min (0.08 h) after intravenous injection. This could be explained on the basis that absorption is instantaneous by the intravenous route and the subsequent fall in the plasma drug concentration may be attributed to the rate of metabolism by the organs of bio-transformation and the rate of elimination by the kidneys or other excretory organs^[15]. The fact that the peak plasma drug concentration after intramuscular administration was attained at 30 min might be attributed to rapid absorption of the drug with the absorption half-life of $0.076 \pm 0.01 \text{ h}$ ($4.56 \pm 0.60 \text{ min}$). In an earlier study, the administration of chloramphenicol to chickens orally at the rate of 30 mg kg^{-1} although was observed to be absorbed rapidly the absorption half-life was ($0.23 \pm 0.02 \text{ h}$) higher than that obtained in the present study^[18].

The pharmacokinetic data in healthy goats treated intravenously and intramuscularly (Table 1) showed that disappearance of chloramphenicol was biphasic with an elimination half-life of $2.45 \pm 1.23 \text{ h}$ and $1.19 \pm 0.07 \text{ h}$, respectively. These half-lives of the drug in goats were relatively shorter than the half-life of 3.5 h reported in cattle^[19], 11.7 h in one day old calves and 4.9 h in 10-12 week old calves^[20]. The longer half-life reported in one day old calves could be due to the underdeveloped hepatic drug metabolising enzyme systems. The significantly ($p < 0.05$) decreased half-life of chloramphenicol following intramuscular injection compare to intravenous in the present study may be due to the increased apparent volume of distribution for chloramphenicol after intramuscular administration in goats observed in the present study ($3.85 \pm 0.46 \text{ L kg}^{-1}$), which may be an indication of considerable tissue penetration of the antibiotic. The relatively smaller volume of distribution for chloramphenicol in cattle reported earlier by Burrows *et al.*^[21] when compared to those in the present study could be due to species differences and/or differences in analytical method. The analytical method used by these workers probably gave higher plasma concentrations of this drug leading to a larger value for area under the curve and a smaller apparent volume of distribution.

The total body clearance of chloramphenicol following intravenous ($1.09 \pm 0.21 \text{ L kg}^{-1} \text{ h}^{-1}$) and intramuscular ($2.24 \pm 0.71 \text{ L kg}^{-1} \text{ h}^{-1}$) injections observed in this study seems to be higher than that of swine ($6.64 \pm 1.52 \text{ mL kg}^{-1} \text{ min}^{-1}$) and dogs ($5.1\text{-}13.2 \text{ mL kg}^{-1} \text{ min}^{-1}$) reported earlier by Mercer *et al.*^[3] and Khazal^[22],

respectively. Bioavailability of chloramphenicol of $80.39 \pm 4.21\%$ after intramuscular administration to goats was higher in this study than that observed by Nouws and Ziv^[23] in ewes. The observed difference may be due to variations in the type of animals used^[23].

This study therefore concludes that, both the intravenous and intramuscular administration of a single dose of chloramphenicol at 25 mg kg^{-1} body weight to Sokoto red goats has resulted in a rapid and adequate serum level of the drug for more than six hours. About 80% of the intramuscularly administered chloramphenicol reached the plasma.

REFERENCES

1. English, P.B., 1961. Plasma and tissue concentrations of chloramphenicol in the pig. Australian Vet. J., 9-11.
2. Watson, A.D.J. and P.J. McDonald, 1976. Distribution of chloramphenicol in some tissues and extravascular fluids of dogs after oral administration. J. Vet. Pharmacol. Ther., 5: 557-559.
3. Mercer, H.D., E.H. George, E. Patricia, D.H. Long and T. Powers, 1978. Drugs residues in food animals. 1. Plasma and tissue kinetics of chloramphenicol in young cross-breed swine. J. Vet. Pharmacol. Therap., 1: 19-36.
4. Eastman, J.W., A.S. Schlingman, M.C. Manning and F.E. Eads, 1952. Chloramphenicol therapy in veterinary medicine. J. Am. Vet. Med. Assoc., 120: 28-29.
5. Rahman, A., 1981. Mastitis in goats and its treatment with leukomyicin (chloramphenicol). Vet. Med. Rev., 2: 183-185.
6. Okeke, G.C., 1996. Diagnosing typhoid fever. Medical Digest, 3: 6-7.
7. Theodorides, V.J., C.J. Dicuollo, J.R. Guarin and J.F. Pagano, 1968. Serum concentration of chloramphenicol after intraluminal administration in sheep. Am. J. Vet. Res., 29: 643-645.
8. Clark, C.E., 1978. Clinical uses of chloramphenicol. Med. Vet. Pract., 59: 889-894.
9. Babale, B.K., 1985. Effects of Fever on Plasma Levels and Pharmacokinetics of Chloramphenicol in Goats. In: Desertification Submitted to Tuskegee Institute, Alabama, USA.
10. Nilsson-Ehle, P., T. Yosikawa and C. Oka, 1960. Quantification of antibiotics using HPLC. Tetracycline, Antimicrobial Agents and Chemotherapy, 9: 754-760.
11. Kakemi, K., T. Arita and S. Ohashi, 1962. Absorption and excretion of drugs IV. Determination of chloramphenicol in blood. J. Pharm. Soc. Japan, 82: 342-347.

12. O'Goreman Hughes, D.W. and L.K. Diamond, 1964. Chloramphenicol in blood, simple chemical estimations in patients receiving multiple antibiotics. *Antibiot. Sci.*, 114: 296-297.
13. Watson, A.D.J., 1979. Plasma chloramphenicol concentration in cats after parental administration of chloramphenicol sodium succinate. *J. Vet. Pharmacol. Ther.*, 2: 123-127.
14. Mason, O.E., S.L. Kaplan, C.J. Baker and D.A. Ritter, 1979. Modification of the coloremtric assay for chloramphenicol in the presence of bilirubin. *Antimicrob. Agents Chemother.*, 15: 544-546.
15. Baggot, J.D., 1980. Distribution of antimicrobial agents in normal and diseased animals. *J. Am. Vet. Med. Assoc.*, 176: 1085-1090.
16. Gibaldi, M. and D. Perrier, 1975. *Pharmacokinetics*. Marcel Dekker Inc. New York, Appendix 4, pp: 293-296.
17. Snedecor, G.W. and W.G. Cochran, 1967. *Statistical Methods* 6th Edn., Oxford and IBH Publishing Company, New Delhi, India.
18. Anadon, A., P. Bringas, M.R. Martinez-Larranage and M.J. Diaz, 1994. Bioavailability, pharmacokinetics and residues of chloramphenicol in the chicken. *J. Vet. Pharmacol. Therap.*, 17: 66-69.
19. Pilloud, M., 1973. Pharmacokinetics, plasma protein binding and dosage of chloramphenicol in cattle and horses. *Res. Vet. Sci.*, 15: 231-238.
20. Reiche, M., M. Mülling and H.H. Frey, 1980. Pharmacokinetics of chloramphenicol in calves during the first week of life. *J. Vet. Pharm Therap.*, 3: 95-106.
21. Burrows, G.E., P.B. Barto and B.R. Weeks, 1986. Chloramphenicol, Lincomycin and oxytetracycline disposition in calves with experimental pneumonic pasteurellosis. *J. Vet. Pharmacol. Therap.*, 9: 213-222.
22. Khazal, K.F., 1982. Comparison of pharmacokinetic parameters of chloramphenicol after analysis of chloramphenicol by gas chromatography, colorimetric and bioassay methods. M.Sc Thesis, Ohio State Univ. Columbus, Ohio.
23. Nouws, J.F.M. and G. Ziv, 1974. Serum chloramphenicol levels and the intramuscular bioavailability of several parental formulations of chloramphenicol in ruminants. *Vet. Q.*, 1: 47-58.