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Pharmacokinetics of Chloramphenicol in Healthy and Water-deprived Goats

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Abstract: A comparative pharmacokinetic study of chloramphenicol (25 mg kg^{-1} intravenous) by Chemical assay in normal and water-deprived Sokoto red goats revealed that the plasma drug concentrations were significantly higher in water-deprived goats. Various pharmacokinetic parameters like Area Under the Curve (AUC), half- life of elimination ($t_{½}\beta$) were significantly lower whereas the total body clearance (Cl) and elimination rate constant (β) were significantly higher in water-deprived goats as compared to normal goats. The mean resident time of the drug also increased from six to nine hours after water deprivation. The higher mean plasma concentration of the drug after water deprivation obtained in the study may indicate the need to reduce the dose of this drug in dehydrated patients to avoid dose-dependent toxicity.

Key words: Chloramphenicol, water-deprived, pharmacokinetic, goats, plasma concentration

INTRODUCTION

Water in the body functions as a solvent for numerous compounds and participates in body temperature regulation, digestion, absorption of digested nutrients, transport of metabolites, excretion of metabolic wastes and maintenance of blood volume. As the body water is lost through the lungs, skin and by excretion in the urine and faeces, so is body water replenished by drinking, consumption in feeds and as product of metabolism in the body. In situations where there is body water deficit, animals attempt to conserve water by desiccation of faeces, concentration of urine, reduction of metabolic rate and preservation of water in the rumen[1]. Bondi[2] emphasised that, animals are more sensitive to water deprivation than food restriction, since loss of twenty percent of body water content may result in death, whereas animals are capable of living after a loss of forty percent of their dry body weight due to starvation.

The effects of water deprivation in sheep, goats and cattle have been reviewed to emphasize the nutritional and clinico-pathological implications[3]. Its effects on elimination of some drugs have been reported. It produced a significant decrease in phenazone clearance (half life in serum) from the body[4].

Water deprivation caused decrease in body water, blood and plasma volumes, extracellular, intracellular and interstitial fluid volumes in ruminants[5-10].

The blood picture as a result of water deprivation showed that plasma or serum sodium concentration increased in most sheep and goat breeds[11-13]. Total serum or plasma proteins and albumin concentration of sheep and goats increased with water deprivation[8,11,12,14-16]. It was observed that, the increased plasma protein in sheep might not be sustained if water deprivation is prolonged, probably due to redistribution of the plasma proteins between the intravascular and extravascular fluid compartments[13]. There was an initial increase in the total plasma protein in water deprived-sheep, due to increased plasma albumin and globulin but later, plasma albumin concentration returned to normal and only the globulin concentration remained increased.

Plasma urea concentration increased after short term water deprivation in sheep[7] and goats[15], but after a long period of water deprivation, the plasma urea concentration returned to normal[13] or decreased[17], perhaps due to the circulation of blood urea to the digestive tract through the saliva and diffusion of blood urea into the rumen and intestine[18]. Plasma creatinine concentration and plasma urea-to-creatinine ratio, were increased after short term water deprivation indicating that plasma urea was increased more than plasma creatinine, probably due to greater renal tubular re-absorption of urea, when deprivation was prolonged, the increase in plasma creatinine concentration was still sustained and urea-to-creatinine ratio had returned to normal due to a decline in the plasma urea concentration[13].

Water intake do produce a profound effect on the pharmacokinetics of many drugs, for this reason the physiological and biochemical changes associated with

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water deprivation and the impact of such on the plasma level and kinetics should be studied[3].

Despite the widespread use of this drug in both man and domestic animals, no relevant data are available on its kinetics in water deprived animals or human patients. The inability of man and animals to drink water is a prominent feature of many infectious diseases and should be an important consideration in the use of this drug, since this condition or water deprivation especially in the arid zone where there is usually periodic drought could affect chloramphenicol elimination and/or metabolism. The study will therefore compare the kinetic profile of Chloramphenicol in healthy and water-deprived goats after a single intravenous injection of the drug.

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 goats were dosed intravenously with chloramphenicol (25 mg kg^{-1}). The same goats were used for both healthy and water-deprived studies with an interval of one month between the experiments. Water was withdrawn from the animals for a period of 24 h and they were treated intravenously with chloramphenicol at the dose of 25 mg kg^{-1}. The animals were thereafter placed on restricted water intake throughout the duration of sample collection. Chloramphenicol was administered into the left jugular vein and blood collected from the right jugular vein.

Sample collection and drug analysis: Three milliliters of blood was collected from the right jugular vein of each of the five goats at 0.0 (15 min prior to drug administration), 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 after chloramphenicol injection. 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.

Chloramphenicol was extracted from all plasma samples chemically using a colourimetric method[19-21].

Pharmacokineic analysis: The phrmacokinetic variables – 0 time intercept (A and B), concentration at zero time (Cp°), Area Under the Curve (AUC), rate constant of distribution (α) and elimination (β), total body clearance (CL), volume of central compartment (VC), volume of distribution ($V^d\beta$) and half-lives of elimination ($t½\beta$) and distribution ($t½\alpha$) were calculated according to standard procedures[22].

Statistical Analysis: Regression analysis and mean±SD were calculated by means of pre-programmed calculator. Test for significance between mean parameters in respect of non-water deprived and water-deprived goats were performed using the student t test and the null hypothesis was rejected at 5% level of probability.

RESULTS

Results showed that there was a significant increase ($p<0.05$) in the peak plasma concentration of the drug (28.15±1.79 μg mL^{-1}) following water deprivation compared to non-water deprivation at 0.08 h after the drug administration. The plasma levels of the drug gradually declined until 0.49±0.10 and 0.35±0.07 μg mL^{-1} were obtained in the normal and water-deprived goats at 6 and 9 h, respectively (Fig. 1 and 2).

The disposition kinetics of the drug in both normal and the water-deprived goats are shown in Table 1. Evaluation of the plots in Fig. 1 and 2 indicate that, the data should fit a two-compartment model. The initial concentration (Cp°) was calculated to be 33.40±4.21 μg mL^{-1}, with distribution rate constant (α) and distribution half-life $t½(\alpha)$ of 6.50±0.85 h^{-1} and 0.13±0.03 h, respectively in the goats before water deprivation. But after the deprivation of water, the initial concentration of chloramphenicol (Cp°) became 34.40±2.11 μg mL^{-1}, with distribution rate constant (α) and distribution half-life $t ½ (\alpha)$, 6.62±0.48 h^{-1} and 0.105±0.02 h, respectively.

The elimination rate constant (β), elimination half-life $t½(\beta)$ and apparent volume of distribution ($V^d\beta$) before

Table 1: Pharmacokinetic parameters for chloramphenicol in goats following intravenous dose of chloramphenicol at 25 mg per kg before and after water deprivation

Parameters	Before water deprivation (n = 5)[a]	After water deprivation (n = 5)[a]
A (μg mL^{-1})	28.10±2.51	28.50±3.01
B (μg mL^{-1})	5.31±0.73	5.90±0.64
C_{po} (μg mL^{-1})	33.40±4.21	34.40±2.11
AUC (h μg^{-1} mL^{-1})	31.22±3.25	18.01±1.45[b]
CL (L kg^{-1} h^{-1})	0.8±0.04	1.39±0.25[b]
V^d_β (L kg^{-1})	4.06±0.32	3.23±0.21[b]
$t_{½}(\beta)$ (h)	3.63±0.51	1.65±0.44[b]
$t_{½}(\alpha)$ (h)	0.13±0.03	0.105±0.02[b]
K_{21} (h^{-1})	1.198±0.26	1.49±0.31[b]
K_{12} (h^{-1})	4.43±0.83	3.65±0.42[b]
K_{el} (h^{-1})	1.07±0.11	1.91±0.34[b]
α (h^{-1})	6.50±0.85	6.62±0.48
β (h^{-1})	0.20±0.06	0.43±0.08[b]
Vc (L kg^{-1})	0.148±0.04	0.726±0.03

a: Data represents mean±S.D., b: Data for goats after water deprivation significantly different from those before water deprivation ($p<0.05$, student's t-test)

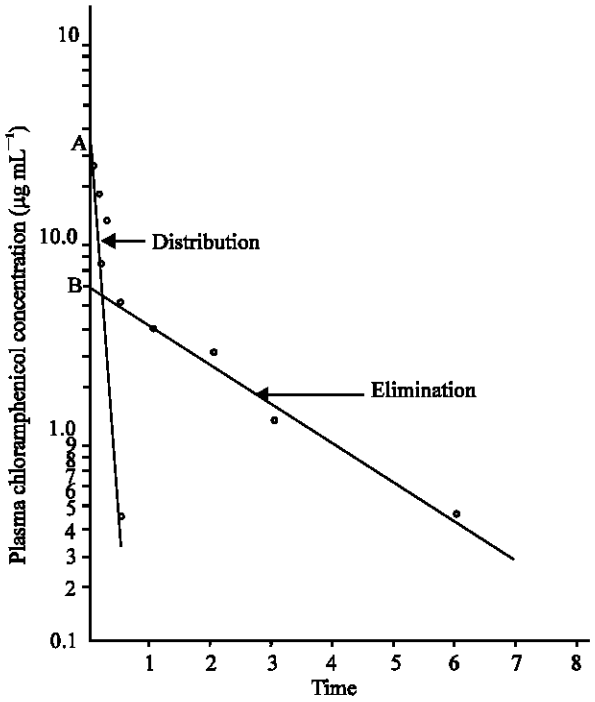

Fig. 1: Semilogrithmic plot of chloramphenicol disappearance in plasma versus time after intravenous administration of a single dose of chloramphenicol (25 mg kg^{-1}) to healthy goats

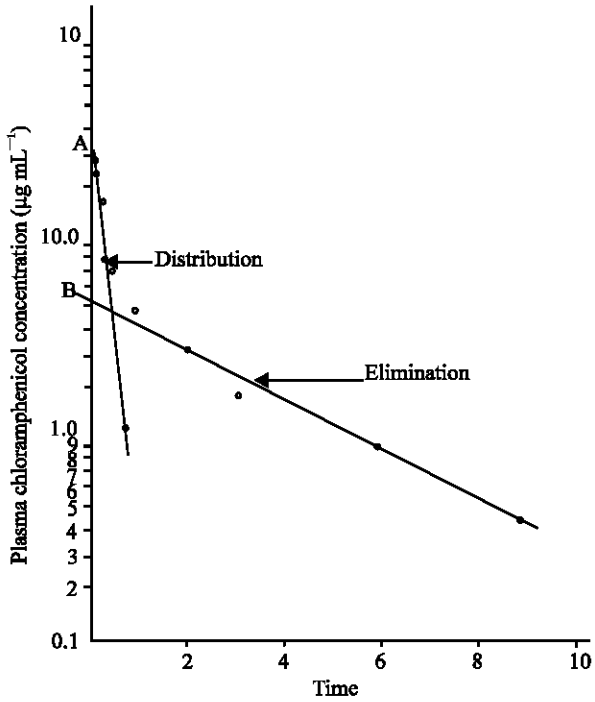

Fig. 2: Semilogrithmic plot of chloramphenicol disappearance in plasma versus time after intravenous administration of a single dose of chloramphenicol (25 mg kg^{-1}) to water deprived goats

water deprivation were calculated to be 0.20±0.06 h^{-1}, 3.63±0.51 h and 4.06±0.32 L kg^{-1} in the Sokoto red goats, respectively. The corresponding values after water deprivation, were 0.43±0.08 h^{-1}, 1.65+0.44 h and 3.23±0.21 L kg^{-1}, respectively for elimination rate constant (β), elimination half-life ($t_{½}\beta$) and volume of distribution ($V^d\beta$).

The total body clearance of chloramphenicol in normal (non-water deprived) goats of 0.8±0.04 L kg^{-1} h^{-1} was significantly lower than 1.39±0.25 L kg^{-1} h^{-1} obtained in goats deprived of water. The distribution rate constant from the peripheral into the central compartment (K_{21}) recorded for goats deprived of water (1.49±0.31 h^{-1}) was higher when compared with that obtained in goats that were not deprived water (1.198±0.26 h^{-1}).

DISCUSSION

The kinetic behaviours of chloramphenicol in non-water deprived and water deprived goats is best described by two-compartment open model. This agrees with the findings in lambs[23], cattle[24], cats[25] and swine[26]. The apparent volume of distribution ($V^d\beta$) relates the drug level in the plasma to the total amount of drug in the body after the attainment of distribution equilibrium. The volume of distribution in non-water deprived goats (4.06±0.32 L kg^{-1}) was significantly higher than that of goats deprived of water (3.23±0.21 L kg^{-1}). This is an indication of more extensive distribution of the drug in goats that were not deprived of water compared to those of water deprived goats. The more extensive distribution in non-water deprived goats may be suggestive of slower elimination of the drug in non water deprived goats. It is a fact that the greater the volume of distribution, the longer the half-life of elimination ($t_{½}\beta$) and slower will the drug be eliminated from the body. Water deprivation is known to decrease the total body water, blood and plasma volumes and extracellular and intracellular fluid volumes[6,8,10,14,27]. Total serum or plasma proteins and albumin concentrations are known to increase with water deprivation[8,12,16]. The increased plasma albumin as a result of water deprivation could enhance drug protein binding and thereby preventing more extensive distribution of the drug especially intracellular and this could be a factor in the differences in volume of distribution of chloramphenicol noticed in water deprived goats in the present study as compared to that of non-water deprived goats. The lower volume of distribution observed following water deprivation may

explain the lower elimination half-life ($t_{½}\beta$) and higher values of elimination rate constant (β) and total body clearance (Cl) obtained in goats deprived of water ($t_{½}\beta$ = 1.65±0.44 h; β = 0.43±0.08 h^{-1}; Cl = 1.39±0.25 L kg^{-1} h^{-1}) compared to non-water deprived value of goats ($t_{½}\beta$ = 3.63±0.51 h; β = 0.20±0.06 h^{-1}; Cl = 0.8±0.04 L kg^{-1} h^{-1}). The observed lower elimination half-life after water deprivation in goats, is quite in contrast to the behaviour of antipyrine in water deprived camels. The half-life of elimination and the mean residence time of antipyrine were significantly prolonged following water deprivation for fourteen days[28]. Water deprivation in the present study was only for twenty-four hours. It has been observed that, the pathophysiological changes associated with water deprivation may differ in short and long term conditions. Plasma urea concentration in sheep increased after short term water deprivation[14] and in goats[15], but after prolonged period of water deprivation, the plasma urea concentration returned to normal[13] or decreased[17]. The higher values of the total body clearance in the water-deprived goats may also have resulted from increased concentration of the drug in the blood and subsequently to the kidney and other organs of elimination due to inadequate blood volume[13]. It is a fact that the amount of the drug cleared from the body per unit time is dependent upon the apparent space available for the distribution of the drug. The larger the volume of distribution, the longer it takes for the drug to be cleared from the body and this may have affected the total body clearance of chloramphenicol in this study. Decreased blood volume as a result of water deprivation may also explain the lower value of distribution half-life ($t_{½}\alpha$) in goats deprived of water ($t_{½}\alpha$ = 0.105±0.02 h) compared to animals that were not deprived of water ($t_{½}\alpha$ = 0.13±0.03 h). However, despite the differences noticed with respect to some kinetic parameters between water-deprived and non-water deprived goats, it is worthy of note that the concentration of the drug at zero time (Cp°) which is the sum of the zero time intercepts for distribution (A) and elimination (B) in non-water deprived goats did not differ significantly from those of water-deprived goats.

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