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Comparative Pharmacokinetics of Intramuscular Ceftriaxone Co-Administered with Acetaminophen in Healthy and Infected Sokoto Red Goats

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Abstract: This study was aimed at finding out if paracetamol influences the pharmacokinetics of ceftriaxone in healthy and salmonella thyphimurium infected Sokoto red goats. In a randomised three-way study, 15 healthy male goats weighing 10-13 kg were divided into three groups of five goats each and each group got either a single intramuscular dose of 1 g ceftriaxone only, 1 g ceftriaxone co-administered with 300 mg paracetamol or 1 g ceftriaxone co-administered with 300 mg paracetamol plus inoculation with *Salmonella thyphimurium*. Non compartmental Pharmacokinetic parameters were measured in plasma samples by microbiological assay. There was a statistically significant ($p<0.01$) decrease in the values of absorption half life (0.51±0.004, 0.17±0.02 and 0.14±0.03 h), maximum plasma concentration (C_{max}) (45.6±0.19, 19±0.32 and 16.5±0.18 μg mL^{-1}), area under the curve (AUC) (144.1±1.711, 42.24±2.11 and 27.50±0.68 μg/h/mL); and also a statistically significant ($p<0.01$) increase in the values of elimination half life (0.58±0.012, 5.34±1.85), Volume of Distribution (Vd) (485.3±15.725, 14382.8±4418.9 and 10467±954.83 mL kg^{-1}) and Clearance (Cl) (578.8±6.880, 1992.72±101.89 and 3039.21±72.1 mL/h/kg) when pharmacokinetic parameters were compared for ceftriaxone alone and ceftriaxone co-administered with paracetamol in healthy and infected Sokoto red goats respectively. This study suggests that paracetamol and *Salmonella thyphimurium* infection alters the plasma disposition of ceftriaxone in healthy and infected Sokoto red goats. We concluded that paracetamol significantly influences the pharmacokinetic profile of ceftriaxone in healthy and infected Sokoto red goats, however further studies are required to confirm these findings and establish the mechanism(s) of interaction.

Key words: Pharmacokinetics, ceftriaxone, acetaminophen, *Salmonella thyphimurium*, Sokoto red goat

INTRODUCTION

The clinical consequences of drug interactions may be antagonistic, additive, synergistic or idiosyncratic, resulting in treatment failure, increased pharmacologic effect or toxic reactions. Pharmacokinetic drug interactions are a consequence of altered levels of exposure to the drug or its metabolites through the alteration of one or more of the pharmacokinetic processes. Monotherapy is desirable but is rarely practicable, extra care should be taken when drugs whose pharmacokinetic interactions are yet been ascertained are to be co-administered. It has been advocated that co-administration of some drugs should be avoided or only in situations where therapeutic drug monitoring can be performed (Pea and Furlanut, 2001). It is essential to examine the influence of altered physiology on the pharmacokinetics of drugs, especially when there are some co-existing pathophysiological conditions affecting drug disposition (Ambros *et al*., 2010). It is therefore, important to study and document the pharmacokinetic outcome of drugs that could possibly be co-administered.

Ceftriaxone is a third generation cephalosporin that is widely used in bacterial infections. Paracetamol is a

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para-aminophenol derivative also known as acetaminophen, a routinely used non-narcotic analgesic, antipyretic agent widely used over the counter for adults and children (Sharma and Srivastava, 1997). It is a common practice to co-administer analgesics and antipyretics for fever and pain in patients receiving antibiotics for infections (Issa *et al*., 2007). Studies have documented the Pharmacokinetic profile of ceftriaxone when administered alone in different conditions (Tiwari *et al*., 2009; Sar *et al*., 2006; Ismail, 2005), Influence of paracetamol and *Salmonella thyphimurium* infection on the plasma kinetics of ceftriaxone in the Sokoto red goat has not been reported to our knowledge. The Sokoto red goat is the most important goat breed in Nigeria, accounting for about 70% of the estimated 34.5 million goats in Nigeria (Osuhor *et al*., 1998), it is the predominant of the three breeds of goats in Nigeria and the most widely used and distributed breed in the northern savannah belts of the country (Ngere *et al*., 1984).

Thus, the purpose of this study was to compare the influence of paracetamol on the plasma kinetics of ceftriaxone in healthy and infected Sokoto Red Goats.

MATERIALS AND METHODS

Animals: Fifteen apparently healthy male Sokoto red goats weighing 10-13 kg were purchased from Dange market in Dange-Shuni Local Government Area of Sokoto State. The goats were housed separately in groups of five and conditioned in pens with concrete floors in the large animal unit of the Faculty of Veterinary Medicine, Usmanu Danfodiyo University Sokoto. They were fed on wheat bran, bean offal, cowpea hay, while water was provided *ad libitum*. Before the commencement of the experiment, the goats were examined and screened to ensure that they were in healthy condition. The animals were evaluated every 24 h after purchase during the period of acclimatization which lasted two weeks.

Study design: The first group received 1 g ceftriaxone only, the second group received 1 g ceftriaxone plus 300 mg paracetamol, while the third group which are a pre-validated model of *Salmonella thyphimurium* infection also received 1 g of ceftriaxone plus 300 mg of paracetamol. All drugs were administered via the intramuscular route. Venous blood samples collected via the jugular vein (5 mL) were drawn pre-dose and at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8,12, 24 and 48 h. The samples were collected in heparinized centrifuge tubes. All the samples were centrifuged, plasma separated and frozen until running the analysis.

Drugs: Paracetamol injection containing 300 mg in 2 mL (PANAGREEN INJECTION) with batch number 93, nafdac registration number 04-8485, manufacturing license No. KTK/28A/445/2001, manufacturing date of February 2007 and expiry date of January 2010, manufactured by GVS LAB, 2, Swamigeha, Ursekarwadi, Dombivl i(E)-421201, India. Generic ceftriaxone injection containing 1 g ceftriaxone powder (PAN-CEFTRIAXONE) with lot/batch number B704128, with manufacturing date of April 2007 and expiry date of April 2010, manufactured by Panpharma Laboratories, Luitre-35133 Fougeres-France.

Inoculation of sokoto red goats with *Salmonella typhimurium*: Stock culture of *Salmonella typhimurium* was used. Each of the ten goats received orally a 10 mL suspension containing 2×10^9 organism mL^{-1}. The goats rectal temperature were recorded daily and signs of ill health noted daily, including appearance, activity, feeding habits and bowel movement. Blood was collected aseptically from the goat's jugular veins for haematological tests. Clinical features indicating infection were noted in the infected goats (Otesile *et al*., 1990).

Pharmacokinetic analysis: Cetriaxone in plasma samples was determined by microbiological assay using agar well diffusion method (Iroha *et al*., 2008). Pharmacokinetic parameters were calculated by inputting the concentration-time data obtained into the pharmacokinetic software PK Solution 2.0 and curve stripping was performed using the least-square technique (Zuluaga *et al*., 2009).

Determination of the regression equation: Pooled plasma from Sokoto red goats was used as diluents to constitute 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 μg mL^{-1} Ceftriaxone solution. Using the agar well dilution technique, the inhibition of the growth of *Escherichia coli* was observed and measured using a vernier calliper. A regression equation $Y = ax+C$ and correlation co-efficient ($R = 0.9935$, $p<0.0001$) was then generated from the concentration response curve using Graph pad instate software.

Statistical analysis: Data was expressed as Mean±SEM. The results were analysed using Graph Pad instate version 3 software and Student's t-test was employed for comparing the means between groups. Differences were considered to be significant at $p\leq0.05$.

RESULTS

Co-administering ceftriaxone with paracetamol in both healthy and *Salmonella thyphimurium* infected goats

caused a fall in values of measured plasma ceftriaxone concentration over time (Table 1).

Half life ($t_{1/2}$): This is a measure of the rate of removal of drug from the body. It is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. In other words, it is the time required to change the amount of drug in the body by one-half during elimination or during a constant infusion. The absorption half life (0.51±0.004, 0.17±0.02 and 0.14±0.03 h), was significantly (p=0.01) decreased, while the elimination half life (0.58±0.012, 5.34±1.85, 2.40±0.28), was increased when values were compared for ceftriaxone alone and ceftriaxone co-administered with paracetamol in healthy and infected Sokoto red goats, respectively. The increase in the elimination half life was only statistically significant (p<0.01) in the healthy goats (Table 2).

Maximum plasma concentration (C_{max}): This refers to the peak serum concentration attained by a therapeutic drug. There was a statistically significant (p<0.01) fall in the value of the C_{max} (45.6±0.19, 19±0.32 and 16.5±0.18 μg mL^{-1}) attained at a T_{max} of 0.7±0.12, 0.5±0.00, 0.5±0.00 h, respectively, when values were compared for ceftriaxone alone and ceftriaxone co-administered with paracetamol in healthy and infected Sokoto red goats, respectively (Table 2).

Table 1: Plasma Ceftriaxone concentrations following a single intramuscular injection alone and when co-administered with paracetamol in healthy and salmonella thyphimurium infected Sokoto red goats

Time (h)	Ceftriaxone alone in healthy goats conc. (μg mL^{-1})	Ceftriaxone+PCM in healthy goats conc. (μg mL^{-1})	Ceftriaxone+PCM in infected goats s (μg mL^{-1})
0.25	32.00±0.51	16.00±0.80	12.00±0.33
0.5	45.00±0.45	19.00±0.31	16.50±0.19
1.0	45.00±0.17	14.70±0.29	7.32±1.70
1.5	37.00±0.38	11.00±0.33	6.40±0.10
2.0	28.50±0.33	7.40±0.24	4.20±0.06
2.5	27.00±0.44	5.70±0.20	3.10±0.08
3.0	25.00±0.95	3.50±0.16	1.70±0.09
4.0	19.00±0.95	1.20±0.13	1.20±0.03
6.0	1.73±0.00	0.80±0.10	0.66±0.03

This table shows the mean concentrations±SEM against time for all animals in the groups (n = 5)

Minimum plasma concentration (C_{min}): Also referred to as the trough serum concentration and is the point of minimum concentration of a drug or therapeutic agent in plasma, this occurs immediately before administering a drug's next dose. In this study the minimum measurable plasma concentration obtained at 6 h post drug administration in the three groups were 1.73+0.00, 0.80+0.10 and 0.66+0.03 μg mL^{-1} (Table 1).

Area under the plasma concentration time curve (AUC): There was a significant (p<0.01) fall in the AUC (144.1±1.711, 42.24±2.11 and 27.50±0.68 μg/h/mL) when values were compared for the three groups (Table 2).

Volume of distribution (V_d): This is a measure of the apparent space in the body available to contain the drug. It relates the amount of drug in the body to the concentration of drug (C) in blood or plasma. Our study revealed a significant (p<0.05) rise in the volume of distribution (485.3±15.725, 14382.8±4418.9 and 10467±954.83 mL kg^{-1}) when values were compared amongst the three groups (Table 2).

Clearance (CL): is a measure of the body's efficiency in eliminating drug. Clearance of a drug is the ratio of the rate of elimination by all routes to the concentration of drug in a biologic fluid. There was a significant increase in the values obtained for clearance (578.8±6.880, 1992.72±101.89 and 3039.21±72.1 mL/h/kg) when pharmacokinetic parameters were compared for ceftriaxone alone and ceftriaxone co-administered with paracetamol in healthy and infected Sokoto red goats, respectively (Table 2).

The plasma kinetic behavior of ceftriaxone when administered alone or when co-administered with paracetamol in healthy and infected Sokoto red goats after intramuscular injection could be best described by a one compartment open model with an absorption, distribution and elimination phase (Fig. 1-3).

Infecting the Sokoto red goats with *Salmonella thyphimurium* infection resulted in a rise in rectal temperature, significant reduction in feed intake,

Table 2: Pharmacokinetic parameters of Ceftriaxone administered alone and co-administered with paracetamol in healthy and infected Sokoto red goats

PK parameters	Ceftriaxone in healthy goats	Ceftriaxone+PCM in healthy goats	Ceftriaxone+PCM in infected goats	p-value
Absorption half life (h)	0.51±0.004	0.17±0.02*	0.14±0.03*	<0.01
Elimination half life (h)	0.58±0.012	5.34±1.85*	2.40±0.28**	<0.01
C_{max} (μg mL^{-1})	45.60±0.19	19.00±0.32*	16.50±0.18*	<0.01
T_{max} (h)	0.70±0.12	0.50±00	0.50±00	
AUC (μg/h/mL)	144.10±1.71	42.24±2.11*	27.50±0.68*	<0.01
AUMC (μg/h*/h/mL)	313.50±6.156	167.14±54.34*	60.14±5.93*	<0.01
Vd (mL kg^{-1})	485.30±15.725	14382.80±4418.9*	10467.00±954.83*	<0.05
Cl (mL/h/kg)	578.80±6.880	1992.72±101.89*	3039.21±72.25*	<0.01
MRT (h)	2.20±0.020	3.80±1.07**	2.20±0.16**	

This table shows mean pharmacokinetic parameters±SEM for all animals in the groups (n = 5). *Significant (p<0.05), **Not significant (p>0.05)

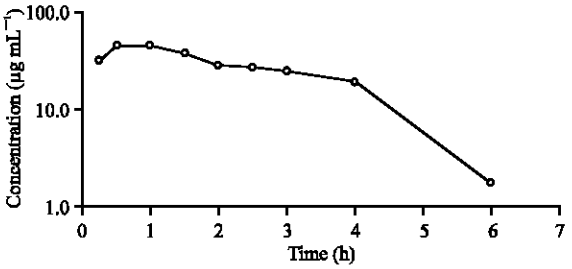

Fig. 1: Semi-Log of concentration-time curve of ceftriaxone following a single intramuscular administration in healthy Sokoto red goats

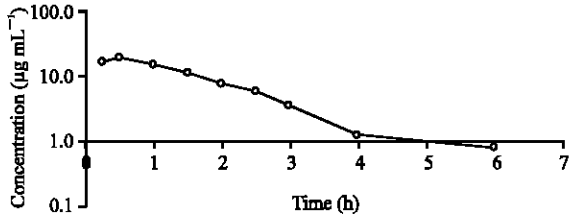

Fig. 2: Semi-Log Plot of concentration-time curve for ceftriaxone plus paracetamol in healthy Sokoto red goats

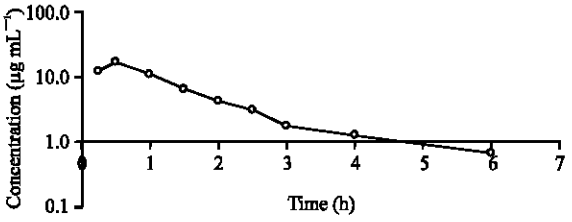

Fig. 3: Semi-Log of concentration-time curve of ceftriaxone following a single intramuscular administration co-administered with paracetamol in infected Sokoto red goats

passage of frequent watery and offensive faeces and lethargy and a significant rise in white blood cell count.

DISCUSSION

The influence of paracetamol on the pharmacokinetics of ceftriaxone in healthy and infected Sokoto red goats was examined in this study. Intramuscular pharmacokinetics of ceftriaxone was investigated in healthy goats after administration of 1 g ceftriaxone. The kinetic behavior of ceftriaxone in healthy goats followed the one compartment open model; the plasma concentration-time curve of ceftriaxone was triphasic with an absorption, distribution and elimination phase. Peak plasma concentration (Cmax) of 45.6±0.19 µg mL^{-1} was observed at (Tmax) 0.7±0.12 h following intramuscular administration in healthy Sokoto red goats. Similar previous studies also reported Cmax in calves, goats and sheeps (20.3±0.92 mg mL^{-1}) (23.6±1.2 mg mL^{-1}) and (23.16±2.94 mg mL^{-1}), respectively (Srivastava and Johal, 1998; Ismail, 2005; Goudah *et al*., 2006). Following intramuscular administration in healthy goats, the elimination half-life (0.58±0.012 h), AUC (144.1±1.71 µg/h/mL) of ceftriaxone was reported.

The pharmacokinetic parameters of ceftriaxone given alone and in combination with paracetamol in healthy and infected Sokoto red goats reveals that paracetamol and *Salmonella thyphimurium* significantly influenced ceftriaxone plasma kinetic behavior, as evidenced in Table 2. In a similar study it was revealed that pharmacokinetics of ceftizoxime was altered by concomitant administration of paracetamol in cross-bred calves (Singh *et al*., 2008). Co-administration of Paracetamol and ciprofloxacin was also reported to cause an increased concentration-time profile of Ciprofloxacin (Issa *et al*., 2007). It was also observed in calves wherein paracetamol was found to increase the AUC of levofloxacin on concurrent administration (Dumka, 2007). Paracetamol has been shown to increase the elimination half-life of oxytetracycline in goats (Manna *et al*., 1993). The co-administration of non steroidal anti inflammatory drugs with cephalosporins has been associated with pharmacokinetic interactions (Chaudhary and Srivastava, 1999). Paracetamol has also been reported to alter the disposition of cephalosporins (Sharma and Srivastava, 1997), findings in the above mentioned studies support our suggestion that paracetamol significantly influence the pharmacokinetics of ceftriaxone in Sokoto red goats. Speculation concerning the mechanism of interaction between analgesics and antimicrobials has focused on drug absorption, distribution, metabolism and elimination. Several drugs are known to alter the hepatic metabolism of other drugs by enzyme induction or inhibition. NSAIDs are known to precipitate renal failure in hepatic disease (Mazoit *et al*., 1987) and inhibit renal production of prostaglandins eventually leading to renal dysfunctions (Rossat *et al*., 1999). Portal hypertension may lead to low peripheral resistance and hyperdynamic circulation due to increased production of vasodilating substances such as nitric oxide (Martin *et al*., 1998). The observed effect of paracetamol on the pharmacokinetics of ceftriaxone may be due to alteration in the rate of drug elimination from body.

In similar studies, infections have been shown to alter the plasma disposition of some drugs (Etuk and Onyeyili, 2006; Burrows *et al*., 1986; Groothuis *et al*.,

1979), these are in support of our suggestion that *Salmonella thyphimurium* infection in Sokoto red goats significantly alters the plasma kinetics of ceftriaxone. These alterations may be due to fever and inflammation induced by the infection. Fever and inflammation occurring in infection may cause an increase in heart rate and cardiac output, increasing blood flow to the liver and kidneys, all these could lead to increase in the rate at which the drug is delivered to both organs which are important sites of drug excretion (Etuk and Onyeyili, 2006).

CONCLUSION

This study suggests that paracetamol and *Salmonella thyphimurium* infection alters the plasma disposition of ceftriaxone in healthy and infected Sokoto red goats. This may imply that a dose adjustment may be necessary when co administering ceftriaxone and paracetamol in healthy and infected Sokoto red goats. The mechanisms of interaction were not studied. Further studies are needed to confirm these findings and establish the mechanism of interaction.

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