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ANIMAL HUSBANDRY & VETERINARY SCIENCE | RESEARCH ARTICLE

Comparative pharmacokinetics of piroxicam in male and female West African Dwarf goats

Emmanuel Itodo Akogwu¹, Saganuwan Alhaji Saganuwan^{1*} and Patrick Azubuiké Onyeyili¹

Abstract: Piroxicam is an anti-inflammatory, analgesic and antipyretic drug. It is presently used for postoperative pain management in ruminants. However, female animals have been reported to be more sensitive to piroxicam. Hence its pharmacokinetic parameters were investigated in West African Dwarf (WAD) goats. Ten goats divided into two groups, each comprised five females and five males were administered piroxicam at predetermined dose of 5 mg/kg body weight via thigh muscle. The blood samples were collected into EDTA bottles before the treatment and thereafter at 0.08, 0.16, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, and 192 h for analysis of piroxicam using a spectrophotometric method at 330 nm wavelength. Concentration maximum ($C_{max} = 543.2 \pm 64.4 \mu\text{g/ml}$), absorption rate constant ($\alpha = 1.2 \pm 0.4 \text{ h}$), and elimination rate constant ($\beta = 0.4 \pm 0.2 \text{ h}$) of the male WAD goats were significantly higher ($p < 0.05$) in comparison with C_{max} ($376.9 \pm 61.2 \mu\text{g/ml}$), α ($0.8 \pm 0.3 \text{ h}$) and β ($0.3 \pm 0.1 \text{ h}$) of the female WAD goats, respectively. The absorption half life ($t_{1/2\alpha} = 1.6 \pm 0.6 \text{ h}$), elimination half life ($t_{1/2\beta} = 5.2 \pm 2.3 \text{ h}$), body clearance ($\text{Cl}_b = 1.1 \pm 0.2 \text{ L/kg/h}$), mean residence time ($\text{MRT} = 7.8 \pm 3.5 \text{ h}$) and mean absorption time ($\text{MAT} = 1.8 \pm 0.4 \text{ h}$) of the female WAD goats were significantly higher ($p < 0.05$) in comparison with $t_{1/2\alpha}$ ($0.9 \pm 0.3 \text{ h}$), $t_{1/2\beta}$ ($2.5 \pm 0.6 \text{ h}$), Cl_b ($0.4 \pm 0.1 \text{ L/kg/h}$), MRT ($0.9 \pm 0.6 \text{ h}$) and MAT ($1.3 \pm 0.5 \text{ h}$) of the male goats respectively. The percentage protein binding capacity in the species was 81.9%. But three out of five female goats were paralyzed. Hence female WAD goats may be more sensitive to piroxicam than male WAD goats.

Subjects: Pharmacology; Pharmacokinetics; Toxicology

Keywords: piroxicam; pharmacokinetics; West African Dwarf goats; intramuscular; paralysis

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PUBLIC INTEREST STATEMENT

The study provides novel information on the movement of piroxicam in the body of WAD goats following administration through the thigh muscle. Piroxicam is a pain reliever, reduces swelling and is used against high body temperature. Piroxicam can reside in the body of WAD goats for upto 8 days; this may pose risk of tissue residues to consumers of such meat. Therefore, consumption of such meat should be in excess of 8 days.

Also a single administration of piroxicam may be sufficient to relieve pain, reduce swelling and decrease high body temperature for a number of days, invariably reducing cost of treatment in WAD goats.

1. Introduction

Piroxicam is a non-steroidal anti-inflammatory drug frequently prescribed and highly utilized in animals to reduce pain, fever and inflammation and in the treatment of different clinical conditions such as rheumatoid disorders and mastitis (Daniel, Regina, & Timothy, 2004). It is bound to plasma proteins, and has a half life of 50 h in humans and is also excreted in urine and faeces (Brayfield, 2004). It has anti-inflammatory, antipyretic and analgesic properties with advantage of once-a-day dosing and so can be used for acute or long term therapy of arthritis. The therapeutic effects are evident early in treatment and the response increases over several weeks (Ballington & Laughlin, 2012). Piroxicam has anti-cancer activity against transitional cell carcinoma of urinary bladder (Knapp, Richardson, Bottoms, Teclaw, & Chan, 1992), offers protection against cerebral ischaemia (Bhattacharya, Pandey, Paul, Patnaik, & Yavagal, 2013), and has hypotensive and sedative effects (Saganuwan & Orinya, 2016). Its CNS effect has been attributed to its ability to undergo keto-enol tautomerism (Saganuwan, 2016a).

Goats play an important role in the economic life of smallholder farmers converting low cost inputs to high valued products; meat, milk and skin (Williamson & Payne, 1978). In Nigeria, West African Dwarf (WAD) goat is kept by crop farmers as a secondary enterprise (Bayern, 1986). Mastitis, post-operative pain, gastrointestinal, reproductive and urinary tract inflammations are treated in WAD goat using piroxicam. Despite the fact that the drug has been licensed in Nigeria, studies have not been carried out on the drug using ruminants. Hence this study aimed to assess the pharmacokinetics of piroxicam in male and female WAD goats.

2. Materials and methods

2.1. Experimental design

Ten goats of both sexes, aged one year old, weighing 10.4 ± 1.30 were randomly selected and assigned into two experimental groups comprising five females and five males. The goats were fed corn offal and fresh grass, and clean water was provided *ad libitum*. All the animals were handled according to international guiding principle for biomedical research involving animals (CIOMS & ICLAS, 2012) as approved by the Ethical Committee, Department of Veterinary Physiology, Pharmacology and Biochemistry, University of Agriculture, Makurdi, Nigeria.

Piroxicam (0.5%) produced by Hambet, Shandong (China), was used for the study at a predetermined dose of 5 mg/kg body weight using human equivalent dose formula (Saganuwan, 2012).

$$\text{Human equivalent dose (HED)} = \frac{\text{Animal dose} \times \text{Animal km}}{\text{Human km}}$$

$$\text{where Km} = \frac{\text{BSA}}{\text{BW}}$$

$$\text{But: Human BSA} = H^{0.528} \times W^{0.528} \times K$$

$$\text{Goat BSA} = \text{BW}^{0.67} \times 10^{-3}$$

km = metabolic constant; BSA = body surface area; BW = body weight.

Each goat was administered 5 mg/kg body weight of intramuscular piroxicam via thigh muscle. The pre-treatment blood samples were collected from the jugular vein into EDTA bottles using 23G needle and 5 ml syringe which served as control ten minutes before drug administration and thereafter at 0.08, 0.16, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, and 192 h for analysis of piroxicam.

2.2. Analytical methods

For preparation of standard, stock solution of piroxicam (1,000 $\mu\text{g/ml}$) was diluted with acetonitrile to obtain serial dilutions containing 2, 4, 6, 8 and 10 μg of piroxicam in 1 ml of solution. One ml of each dilution was again diluted to 5 ml with acetonitrile. To this solution 1 ml of blood from an

animal undosed piroxicam was added. The tubes were then centrifuged at 2,500 rpm for 15 min and 4 ml of supernatant was removed and 0.2 ml of 1.47 M aqueous perchloric acid (HClO_4) was added to it. The absorbances of these solutions were measured with a spectrophotometer at 330 nm against a blank prepared in the same manner without piroxicam. The absorbances were then plotted against concentration of piroxicam (Nagabhushanam & Sudha, 2010).

For analysis of blood piroxicam, added was acetonitrile (5 ml) to 1.0 ml of the blood in a centrifuge tube and mixed. The tubes were then centrifuged at 2,500 rpm for 15 min and 4 ml of the supernatant was collected into a dry test tube and 0.2 ml of 1.47 M aqueous HClO_4 solution was added and mixed. The absorbance of the resulting solution was measured at 330 nm against a blank prepared in the same manner with blood collected before drug administration (Nagabhushanam & Sudha, 2010). The minimum detection limit of the assay was 5 $\mu\text{g/ml}$ (Nagabhushanam & Sudha, 2010).

2.3. Pharmacokinetic modelling approach

The linear calibration curve of piroxicam in blood within the range of 2–10 $\mu\text{g/ml}$ was obtained by plotting percentage absorbance against drug concentration. The correlation coefficient (R^2) was greater than 0.92. The concentration of piroxicam in blood was calculated using the formula indicated below:

$$\text{Concentration of drug} = \frac{\text{Concentration of standard} \times \text{Optical density of drug}}{\text{Optical density of standard}}$$

The pharmacokinetic parameters for individual animals were calculated using established pharmacokinetic equations (Agbo, Saganuwan, & Onyeyili, 2016; Baggot, 2001; Saganuwan, 2012).

2.4. Statistical analysis

Blood concentrations and pharmacokinetic parameters were presented as mean \pm standard error of mean (SEM). Test for significance between the parameters in respect of female and male WAD goats

Figure 1. Mean plasma concentration-time curves of piroxicam (5 mg/kg) following a single intramuscular administration in male and female WAD goats.

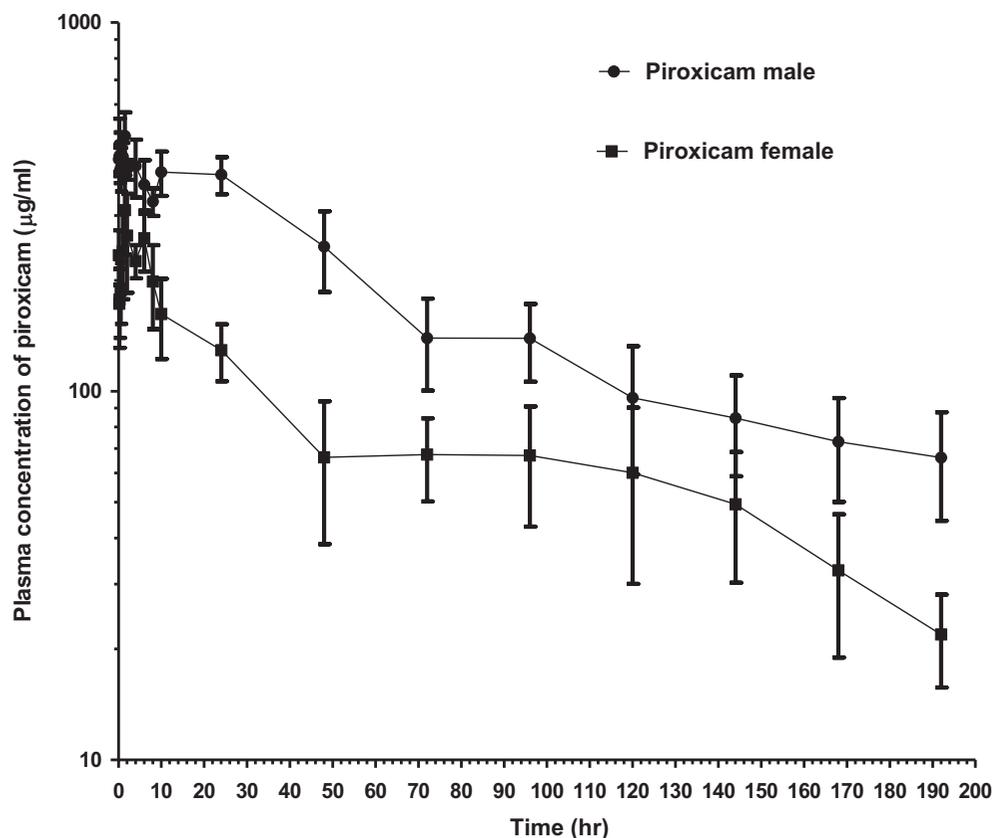


Table 1. Pharmacokinetic parameters of piroxicam (mean ± standard error) from male and female West African Dwarf goats following intramuscular treatment at 5 mg/kg body weight (n = 10)

Kinetic parameters	Male (n = 5)	Female (n = 5)	p-value
A (µg/ml)	271.9 ± 71.9	89.4 ± 20.3	p < 0.05
B (µg/ml)	135.1 ± 100.9	132.6 ± 68.5	p > 0.05
C _{max} (µg/ml)	543.2 ± 64.4	376.9 ± 61.2	p < 0.05
T _{max} (h)	1.2 ± 0.7	1.5 ± 0.7	p > 0.05
V _d (area) (L/kg)	1.5 ± 0.5	1.1 ± 0.5	p > 0.05
α (1/h)	1.2 ± 0.4	0.8 ± 0.3	p < 0.05
β (1/h)	0.4 ± 0.2	0.3 ± 0.1	p < 0.05
t _{1/2α} (h)	0.9 ± 0.3	1.6 ± 0.6	p < 0.05
t _{1/2β} (h)	2.5 ± 0.6	5.2 ± 2.3	p < 0.05
Cl _b (L/kg/h)	0.4 ± 0.1	1.1 ± 0.2	p < 0.05
MRT (h)	0.9 ± 0.6	7.8 ± 3.5	p < 0.05
MAT (h)	1.3 ± 0.5	1.8 ± 0.4	p < 0.05
AUC _{0-192h} (mg/L/h)	22.8 ± 6.9	14.8 ± 4.0	p < 0.05
AUC _{0-∞} (mg/L/h)	32.1 ± 5.3	15.0 ± 4.0	p < 0.05
AUMC (mg h ² /L)	91.9 ± 22.2	50.4 ± 18.9	p < 0.05
Plasma protein binding (%)	81.9	81.9	p > 0.05

Notes: A = absorption phase; B = elimination phase; C_{max} = peak concentration; T_{max} = peak time; V_d (area) = volume of distribution area; α = absorption rate constant; β = elimination rate constant; t_{1/2α} = absorption half life; t_{1/2β} = elimination half life; Cl_b = clearance; MRT = mean residence time; MAT = mean absorption time; AUC₀₋₉₆ = area under the curve zero to 96 h; AUC_{0-∞} = area under the curve zero to infinity; AUMC = area under the moment curve.

administered piroxicam (5 mg/kg) was performed using paired samples Student's *t* test at 5% level of significance (Gravetter & Wallnau, 2004).

3. Results

Figure 1 shows pharmacokinetic profile of intramuscular administration of piroxicam at dose level of 5 mg/kg body weight in both male and female WAD goats. The drug increased from 425.9 ± 32.4 to 466.1 ± 82.7 µg/ml after 10 min and started dropping to 435.4 ± 68.5 µg/ml after 15 min and finally dropped to 60.9 ± 13.8 µg/ml after 192 h in males. But in female goats, there was plasma concentration of 233.9 ± 39.4 µg/ml 5 min post administration of piroxicam which dropped to 172.7 ± 41.4 µg/ml 10 min after, then rose to 177.5 ± 37.9 µg/ml after 15 min and 187.8 ± 35.3 µg/ml after 30 min and finally dropped to 21.9 ± 5.4 µg/ml after 192 h. The plasma protein binding capacity of piroxicam in the goats was 81.9%. The estimated pharmacokinetic parameters are presented in Table 1.

4. Discussion

The pharmacokinetic profiles of intramuscular piroxicam in male and female WAD goats fit two compartment open model (Figure 1). The increased C_{max} (543.2 ± 64.4 µg/ml) of male WAD goats as compared with the C_{max} (376.9 ± 61.2 µg/ml) of the female goats shows that higher concentration of intramuscular piroxicam was achieved in male WAD goats. However, the values of C_{max} are lower in male and female rat using intramuscular route (Park, Ma, Jang, Son, & Kang, 2014). The significantly increased areas under the curve AUC_{0-192h} (22.8 ± 6.9 mg/L/h) and AUC_{0-∞} (32.1 ± 5.3 mg/L/h) of the male goats as compared to the AUC_{0-192h} (14.8 ± 4.0 mg/L/h) and AUC_{0-∞} (15.0 ± 4.0 mg/L/h) of the female goats observed in the current study agree with the report of Kendeigh (1945) indicating that male animals retain more drugs than female animals because of their high body fat component.

The increased elimination half life (t_{1/2β} = 5.2 ± 2.3 h) and mean residence time (MRT = 7.8 ± 3.5 h) of female goats in comparison with t_{1/2β} = 2.5 ± 0.6 h and MRT (0.9 ± 0.6 h) of male goats shows that

piroxicam is eliminated faster in male goats as compared to female goats. Since piroxicam causes hyperbilirubinaemia (Abatan, Lateef, & Taiwo, 2006) and bilirubin competes for same binding site with piroxicam, the elimination of piroxicam may likely be delayed, and so accounting for 81.9% plasma protein bound in the current study. The $t_{1/2\beta}$ = (13.0 ± 2.7 h; 14.5 ± 5.6 h) and MRT (25.9 ± 5.5 h; 27.7 ± 8.2 h) are higher in female but lower (8.3 h) in male rats (Saidu & Fada, 1989). Body clearance was lower in male (Clb = 0.4 ± 0.1 L/kg/h) as compared to female (1.1 ± 0.2 L/kg/h) WAD goats and higher in both sexes in comparison with young (0.05 ± 0.01 L/kg/h) and adult rats 0.02 ± 0.003 L/kg/h as well as male (0.02 L/kg/h) and female (0.006 L/kg/h) rats, respectively (Boudinot, Funderburg, & Douglas Boudinot, 1993).

The $t_{1/2\beta}$ of piroxicam (5 mg/kg) in male (2.5 ± 0.6 h) and female (5.2 ± 2.3 h) WAD goats are lower than that of male (13.3 h) and female (40.8 h) rats administered 0.5 and 5 mg/kg body weight of piroxicam, intravenously (Roskos & Boudinot, 2006). The half-life (2–9 h) of piroxicam at 3 and 10 mg/kg body weight in rabbit, rats and rhesus monkey and 45 h in beagle dog (Hobbs & Twomey, 1981) are higher than that of WAD goats in the current study (2.5–5.2 h). The plasma half-life of piroxicam (1–2 mg/kg per os) is 1.7 h in mice (Milne & Twomey, 1980), and the maximum tolerated dose in dog was 1 mg/kg every 48 h. But the acceptable dose for dog is 0.3 mg/kg per os every 24 h (Knapp, Richardson, Bottoms, Teclaw & Chan, 1992). The time of peak concentration in rats is 2.56 h (Tagliati, Kimura, Nothenberg, Santos, & Oga, 1999), signifying that routes of administration, dosage forms and species variation can adversely affect pharmacokinetic profile of piroxicam. However Mirza, Miroshnyk, Habib, Brausch, and Hussain (2010) reported that the differences in the pharmacokinetic parameters may be due to routes of administration (Mirza et al., 2010). Since about 99% of piroxicam is bound to proteins, its distribution is limited primarily to the extracellular spaces. Nevertheless, it readily penetrates the synovial fluid and is found in concentrations that are approximately 40% (Callin, 1988) or 50% (Trnavská, Trnavský, & Žlnay, 1984) of those in plasma.

The apparent volume of distribution, a value typical for most non steroidal anti-inflammatory drugs (Olkola, Brunetto, & Mattila, 1994; Verbeeck, Richardson, & Blocka, 1986) was not different between male and female WAD goat. As the concentration of the drug increases, the number of water molecules to dissolve it decreases. This results in a concentration-dependent high-energy shift of the absorption maximum (Banerjee & Sarkar, 2002). However Okafor, Remi-Adewumi, and Fadason (2014) reported that 5 mg/kg body weight of piroxicam can significantly reduce pain in orchidectomised goats. This process may be by penetration through blood brain barrier which is positively correlated with lipid solubility at high dose or negatively correlated with hydrogen bonding or due to damage to meninges (Saganuwan, 2016a). The paralysis of the affected goat found in this trial agrees with the report of Saganuwan and Orinya (2016) indicating that piroxicam has central nervous system locomotor effects which might be caused by higher dose of piroxicam (5 mg/kg) administered in the current study as compared to the reported values in cat (0.56 mg/kg), baboon (0.53 mg/kg), micro-pig (0.3 mg/kg), mini-pig (0.3 mg/kg), rat (1.7 mg/kg), guinea-pig (1.8 mg/kg), marmoset (1.8 mg/kg), monkey (1.6 mg/kg), hamster (2.6 mg/kg), mouse (3.6 mg/kg) and dog, 0.5 mg/kg, respectively (Saganuwan, 2014). However, piroxicam reaches local tissues by direct penetration (Yingjian et al., 2002). Saganuwan (2016b) reported that piroxicam in the body could be converted to central nervous system acting drugs. The pharmacokinetic profiles (C_{max} , α , β) of piroxicam intramuscular (5 mg/kg) are significantly higher in male WAD goats as compared to female WAD goats that showed increased $t_{1/2\alpha}$, $t_{1/2\beta}$, Clb, MRT and MAT, respectively. Hence, it can be concluded that female WAD goats are more sensitive to piroxicam than male WAD goats. Moreso, 5 mg/kg body weight of the drug can last more than 192 h (8 days) in the WAD goats.

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Competing Interest

The authors declare no competing interest.

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