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Original article

Effects of diminazene aceturate on flip-flop plasma pharmacokinetics of piroxicam in dogs

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ABSTRACT

Objectives: Pain, fever and inflammation associated with protozoan infections caused by Trypanosomes, Babesia, Entamoeba, Leishmania and Pneumocystis have necessitated the search for polypharmacy,that could be used for treatment of protozoan infections in dogs.

Methods: Randomized cross-over controlled trial was adopted for kinetic study of piroxicam (3.5 mg/kg) and piroxicam (3.5 mg/kg) administered with diminazene aceturate (3.5 mg/kg) in Nigerian indigenous dogs. Ten dogs comprised 5 males and females, each of about 8 ± 2 months and weighed 10 ± 0.5 kg were administered piroxicam, after one month the dogs were administered piroxicam and diminazene aceturate at different thigh muscles. Single dose was administered to avoid toxicity. Blood samples were collected at 0, 0.08, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 24, 48, 72 and 96 h for plasma analysis of piroxicam.

Results: Findings have shown that piroxicam was significantly ($p < 0.05$) slowly absorbed (5.823 ± 1.46 h^{-1}) and eliminated (0.935 ± 0.75 h^{-1}) as compared to piroxicam/diminazene aceturate group (7.405 ± 1.75 h^{-1}) and (0.137 ± 0.10 h^{-1}), respectively. Concentration maximum (C_{max} = 12.659 ± 0.85 μg/ml), peak time (T_{max} = 13.675 ± 9.21 h), absorption half-life ($T_{1/2\alpha}$ = 0.016 ± 0.04 h), elimination rate constant (β = 0.137 ± 0.10 h^{-1}), area under curve zero to infinity ($AUC_{0-\infty}$ = 778.885 ± 66.99 mg/L/h), area under moment curve (AUMC = 9820.140 ± 5.33 mg/h^2/L), fraction absorbed zero to 96 h (Fab_{0-96h} = 7.505 ± 0.00%) were significantly lower in piroxicam/diminazene aceturate ($p < 0.05$) as compared to C_{max}(18.560 ± 2.97 μg/ml), T_{max} (45.000 ± 11.49 h), $T_{1/2\alpha}$(0.250 ± 0.08 h), β (0.935 ± 0.75 h^{-1}), $AUC_{0-\infty}$ (814.472 ± 86.43 mg/L/h), AUMC (36274.840 ± 9010.44 mg/h^2/L), and Fab_{0-96h} (7.848 ± 0.00%) in the piroxicam treated group, respectively. The elimination half-life was significantly lower ($p < 0.05$) in piroxicam (33.634 ± 9.34 h) as compared with piroxicam/diminazene aceturate (34.850 ± 11.94 h) treated group.

Conclusion: Hence piroxicam displays flip-flop phenomenon of absorption, and could be coadministered with diminazene aceturate at single or twice dose for treatment of trypanosomosis, amoebiasis, leishmaniasis, pneumocytis and babesiosis in dogs.

1. Introduction

Diminazene aceturate is an aromatic diamidine which consists, two amidinophenyl moieties linked by a triazene. It is the most widely used for treatment of trypanosomosis and babesiosis in domestic livestock. It is injectable with narrow safety margin, and appropriate dose is caculated (Riviere and Papich, 2017). Animals that are hypersensitive to diminazene aceturate or phenazone as well as patients with impaired renal and hepatic function should not be administered the drug (Fussanger, 1995). Diminazene aceturate is used in the treatment of trypanosomosis in dogs at a dose of 3.6-7 mg/kg intramuscularly every two weeks, and in horses, cattle, sheep and goats at 3.5 mg/kg intramuscularly once, and in the treatment of babesiosis in dogs at 3.5 mg/kg, repeated after 24 h respectively. Diminazene aceturate is used in the treatment of cytauxzoonosis in cats at a dose of 3–5 mg/kg intramuscularly at a time or 2 mg/kg intramuscular injection repeated in one week (Holman and Snowden, 2009). The drug also has an anti-

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inflammatory property which is yet to be fully proven (Trapp et al., 2006).

Piroxicam is a non-steriodal anti-inflammatory drug (NSAID) used to treat pain, fever and inflammation. It is highly potent with half-life of over 50 h, administered once daily. It exists in two different interconvertible crystal polymorphs with melting point of 196–198 °C and 199–201 °C, respectively. Piroxicam inhibits cycloxygenase (COX), the enzyme that catalyzes the conversion from arachidonic acid to prostaglandins (PGs) that mediate pain. Piroxicam crosses the blood brain barrier which makes it very potent in reducing fever (Baltoyiannis et al., 2001). However there is no information on the effect of diaminazene aceturate on kinetics of piroxicam in Nigeria indigenous dogs. Akogwu et al. (2017a, b,c) carried out similar work in goats using piroxicam and sulphadimidine. Immunogenic potential and different physicochemical properties of the two drugs could be of therapeutic benefit. The present study was carried out, with an intent to identifying effect of diaminazene aceturate on kinetics of piroxicam, following intramuscular administration in dogs.

2. Materials and methods

2.1. Drugs

Diminazene aceturate and piroxicam produced by Hambet, Shandong, China were used for the studies at single dose of 3.5 mg/kg body weight.

2.2. Determination of therapeutic dose of piroxicam

Human equivalent dose formula was used to determine therapeutic dose of piroxicam (3.5 mg/kg) in dogs (Saganuwan, 2012).

$$\text{Human Equivalent Dose (HED)} = \frac{Animal\ \ Dose \times Animal\ \ Km}{HumanKm}$$

$$\text{Whereas Metabolism constant } (k_m) = \frac{Body\ \ Surface\ \ Area}{Body\ \ weight}$$

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

Dog BSA = $H^{0.528} \times W^{0.528} \times K$ (multiply height by 2).

K_m = metabolic constant; BSA = Body surface area; K (constant) =0.14; H =height; W = weight.

2.3. Experimental animals

The study was conducted in the Department of Veterinary Phamacology and Toxicology laboratory, Collage of Veterinary Medicine, Federal University of Agriculture Makurdi, Nigeria. Ten apparently healthy Nigerian indigenous dogs of both sexes, aged 8 ± 2 months, and weighing 10 ± 0.5 kg were purchased from dog market in Makurdi, and used for the experiment. The animals divided into two groups of 5 each, were kept in a clean kernel, and fed normal rice, beans, semovita, fish and meat thrice daily. Clean water was provided *ad libitun*. The dogs acclamatized for 14 days were handled according to the international guiding principles on biomedical research involving the use of animals (CIONs and ICLAS, 2012), as approved by the Ethical Committee, Collage of Veterinary Medicine, Federal University of Agriculture Makurdi, Nigeria.

2.4. Experimental design

Modified randomized cross-over controlled design was adopted for this study. Each of the animals was randomly picked for administration of the drugs. The group of dogs administered piroxicam was used as control (Akogwu et al., 2017a).

2.5. Drug administration and sampling

Ten dogs (5males; 5 females) were injected piroxicam (3.5 mg/kg) in the thigh muscles. After one month, the same group of dogs was injected in the separate thigh muscles, diminazene aceturate (3.5 mg/kg), followed by piroxicam at 3.5 mg/kg body weight. Modified arithmetic method was used for blood sampling (Akogwu et al., 2017b). Blood samples were collected ten minutes before drug administration, from the cephalic vein using a 23G needle, and 5 ml syringe into ethylene diamine tetra acetate (EDTA) bottles at 0.0, 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96 h, respectively, for analysis of piroxicam. The samples collected were immediately centrifuged at 5000 revolution per minute (rpm) for 5 min. Plasma was obtained using a micropipette, placed in cryogenic vials, and stored at −20 °C until analyzed.

2.6. Preparation of standard

Piroxicam (1,000 mg/ml) stock solution was diluted with acetonitrile to obtain serial dilutions containing 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 µg of piroxicam in 1 ml of solution. One millitre of each was again diluted with 5 ml of acetonitrile. One millitre of plasma was added to each of the solutions. The tubes were centrifuged at 2500 rpm for 15 min, and 1 ml of supernatant was removed and 0.1 ml of 1.47 M aqueous perchloric acid ($HCLO_4$) added. A spectrophotometer at 330 nm was used to measure the absorbance against a blank prepared in same manner with piroxicam and piroxicam/diminazene aceturate. The absorbance was plotted against concentration of piroxicam and diminazene aceturate (Akogwu et al., 2017a,b).

2.7. Analysis of piroxicam

The revised method of Nagabhushanam and Sudha (2010) was adopted. Acetonitrile 2.5 ml was added to 1 ml of serum in centrifuge tubes, mixed gently and properly. The tubes were centrifuged at 2500 rpm for 15 min, and 1 ml of the supernatant was added to 0.1 of 1.47 M aqueous perchloric acid solution. The mixture was properly shaken and measured at 330 nm using a spectrophotometer, to obtain the absorbance against a blank prepared in the same manner with plasma. Minimum limit of detection was 2 µg/ml (Akogwu et al., 2017a,b).

2.8. Calculation of pharmacokinetic parameters

The pharmacokinetic parameters for individual animals were calculated manually using established non-compartmental pharmacokinetic equations (Baggot, 2001) as modified by Saganuwan (2020). The fractions of doses absorbed were determined according to the method of Saganuwan (2012).

i. $C_{max}$was determined from graph
ii. $T_{max}$was determined from graph
iii. Absorption rate constant (α) was calculated as follows;

$$a = \frac{InC\max - InC\min}{T\min - T\max}\left(\frac{1}{h}\right)$$

iv. Absorption half-life ($T_{1/2}$) $= \frac{0.693}{a} hr$
v. Mean absorption time (MAT)$= \frac{T1/2a}{0.693} hr$
vi. Elimination rate constant (β) was calculated as: $\beta = \frac{InCmax - InCmin}{Tmin - Tmax}\left(\frac{1}{h}\right)$
vii. The values of microconstant were used to determine the following parameters; Elimination half- life ($T_{1/2\beta}$) $= \frac{0.0693}{\beta} 1/hr$

viii. Area under curve: $AUC_{0\text{-}n} = \sum\{C_{p1} + C_{p2} \times (t_2\text{-}t_1) + \{C_{p2} + C_{p3} \times (t_3\text{-}t_2)\} + \ldots\ldots$(mg/L/hr)

ix. Area under the curve Zero to infinity ($AUC_{0\text{-}\infty}$) = $AUC_{0\text{-}96} + \frac{Cplast}{\beta}$ (mg/L/h)

x. Body clearance (Clb = Vd × β (L/kg/hr)

xi. Volume of distribution area (Vd) = $\frac{Clb(L/kg)}{\beta}$

xii. Mean residence time (MRT) = $\frac{Vd}{Clb}(hr)$

xiii. Area under moment curve = MRT × AUC (mg/L)

Table 1
Plasma concentration of piroxicam alone and piroxicam co-administered with diminazene aceturate in dogs.

Time (hr)	Piroxicam alone	Diminazene aceturate/Piroxicam
0.08	4.960 ± 0.77	5.030 ± 0.94
0.25	5.240 ± 0.99	4.630 ± 1.56
0.5	4.740 ± 0.95	8.270 ± 0.98[a]
1	5.830 ± 0.92	5.470 ± 1.02
1.5	9.190001 ± 1.79	6.160 ± 1.45[b]
2	5.800 ± 1.49	8.870 ± 1.47[a]
3	5.720 ± 0.93	10.260 ± 0.36[a]
4	6.850 ± 0.87	5.910 ± 0.78[b]
6	6.680 ± 0.87	10.230 ± 0.36[a]
8	9.460 ± 3.34	8.700 ± 0.99
10	8.816 ± 2.43	8.060 ± 1.26
12	7.730 ± 1.65	5.780 ± 1.26[b]
24	7.060 ± 1.25	7.640 ± 0.95
48	7.860 ± 1.00	6.660 ± 1.13
72	8.700 ± 2.74	7.800 ± 1.54
96	9.050 ± 1.32	9.940 ± 0.56

xiv. Fraction of absorbed drug (Fad) = $\frac{Amount\ of\ drug\ absorbed}{Vd} = (\alpha \times \beta \times AUC0 - 96\ \text{h})$

Fractions of piroxicam absorbed from zero to 96 h and zero to infinity were calculated and translated to percent drug absorbed.

Xv. Bioavalability of absorbed fraction (Faf) = $\frac{AUC\ \ piroxicam/diminazene\ \ (iv)}{AUC\ \ piroxicam\ \ (iv)}$

2.9. Statistical analysis

Plasma kinetic data were presented both in graphical and tabular form. Plasma concentrations and pharmacokinetic parameters for piroxicam and piroxicam/diminazene aceturate were presented as mean ± standard error of mean (SEM). Kinetic parameters were analyzed using students *t* test paired at 5% level of significance. The concentrations of piroxicam and piroxicam/diminazene aceturate were analyzed using two-way analysis of variance (ANOVA), and least significant difference was detected at 5% level (Zar, 2008).

3. Results

3.1. Plasma concentration–time profile of piroxicam alone and piroxicam co-administered with diminazene aceturate in Nigerian indigenous dogs following intramuscular administration

The concentration of piroxicam and piroxicam/diminazene aceturate over a range of time is presented in Table 1. The concentra-

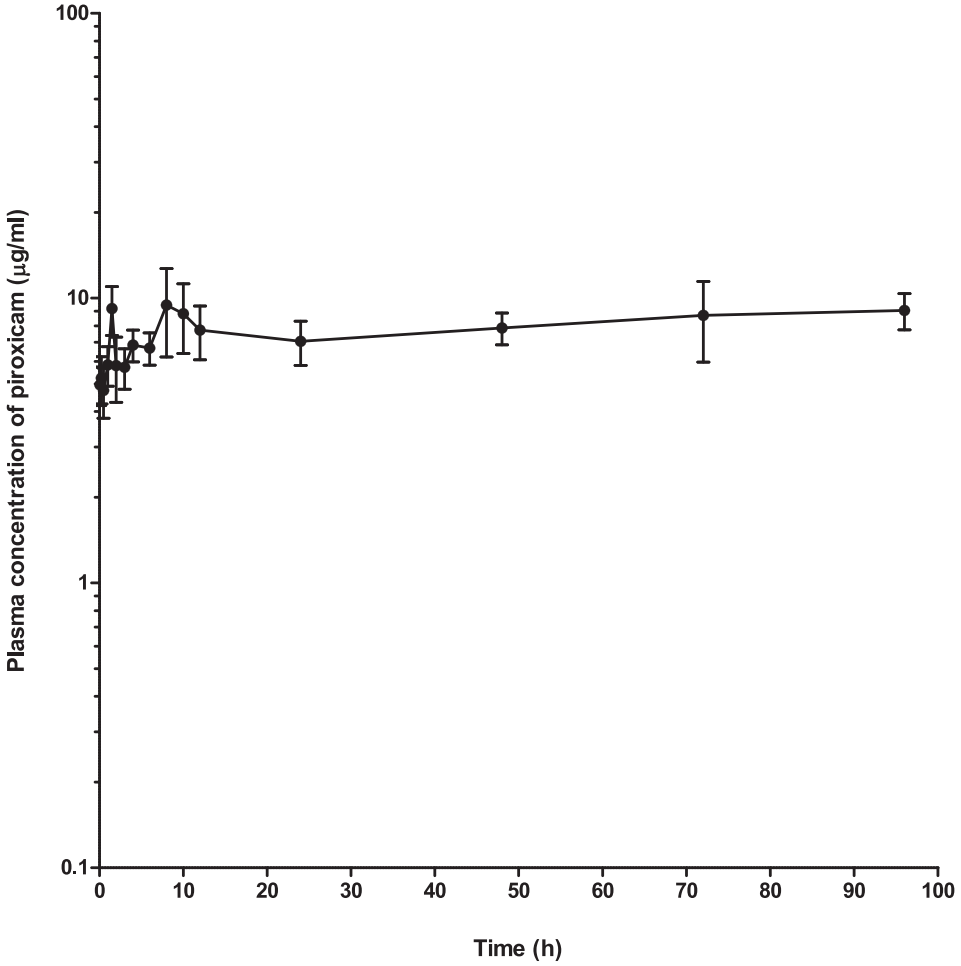

Fig. 1. Mean plasma concentration–time curve of 3.5 mg/kg intramuscular piroxicam alone in dogs (n = 10).

tions were not different, significantly ($p > 0.05$) at 0.08 and 0.25 h. However, the concentration was significantly higher ($p < 0.05$) at 0.5 h (8.270 ± 0.98), 2 h (8.870 ± 1.47), 3 h (10.260 ± 0.36 μg/ml) in piroxicam/ diminazene aceturate group as compared to 4.70 ± 0.95, 5.500 ± 1.49 and 6.680 ± 0.87 μg/ml in the piroxicam group respectively. Nevertheless at 12 h, the concentration of piroxicam /diminazene aceturate dropped significantly ($p < 0.05$) to 5.780 ± 1.2 μg/ml as compared to piroxicam group (7.730 ± 1. 65 μg/ml), respectively (Table1). Plasma concentration–time profile of piroxicam alone (Fig. 1), piroxicam/diminazene aceturate (Fig. 2) and combination of piroxicam and piroxicam/diminazene aceturate (Fig. 3) obey two compartmental model of kinetics that is flip-flop in nature.

3.2. Pharmacokinetic prarameters of intramuscular piroxicam and piroxicam/diminazene aceturate in Nigerian indigenous dogs

The calculated pharmacokinetic parameters of piroxicam and piroxicam/diminazene aceturate are presented in Table 2. Plasma concentration maximum (C_{max} = 12.659 ± 0.85 μg/ml), time peak (T_{max} = 13.675 ± 9.21 h), absorption half-life ($T_{1/2}\alpha$ = 0.016 ± 0.04 h), elimination rate constant (β = 0.137 ± 0.10 h^{-1}), area under curve from zero to infinity ($AUC_{0-\infty}$=778.885 ± 66.99 mg/L/h) and area under moment curve (AUMC = 98200.140 ± 5.33 $mg/h^2/L$) were significantly lower ($p < 0.05$) in piroxicam/diminazene aceturate treated group as compared to C_{max} (18.560 ± 2.97 μ/mg), T_{max}(45000 ± 11.49 h), $T_{1/2}\alpha$(0.250 ± 0.00 h), β(0.935 ± 0.75 h^{-1}) $AUC_{0-\infty}$(814.472 ± 86.43 mg/L/h) and AUMC(36274640 ± 9010 $mg/h^2/L$) in the piroxicam treated group respectively. However, absorption rate constant (α = 7.405 ± 1.75 h^{-1}), mean absorption time (MAT = 0.658 ± 0.45 h), area under curve AUC_{0-96h} (734.832 ± 63.20 mg/L/h), volume of distribution (Vd = 0.311 ± 0.16 L/kg) and mean residence time (MRT = 106.561 ± 54.84 h) were significantly higher ($p < 0.005$) in piroxicam/diminazene aceturate group as compared with α(5.823 ± 1.46 h^{-1}), MAT (0.361 ± 0.11 h) Vd (0. 206 ± 0.08 L/kg) and MRT (49.793 ± 13.43 h) in the group treated with piroxicam alone respectively (Table 2).

4. Discussion

The slow elimination rate of piroxicam and piroxicam/diminazene aceturate in the present study agrees with the report, indicating that antinflammatory and antibiotic agents could display flip-flop kinetics, which occurs when the absorption rate is slower than the elimination rate, hence a long duration sampling is required. Dosage formulations, chemistry of drugs, excipient and extravascular physiology could cause flip-flop phenomenon (Yanaz et al., 2011), characterized by slower absorption rate constant (5.823 ± 1.46 h) and elimination rate constant (0.935 ± 0.75 h) for piroxicam alone, as compared to 7.405 ± 1.75 h and 0.137 ± 0.10 h for piroxicam/diminazene aceturate, respectively. The rate-limiting factor of intramuscular absorption is the deposit site from

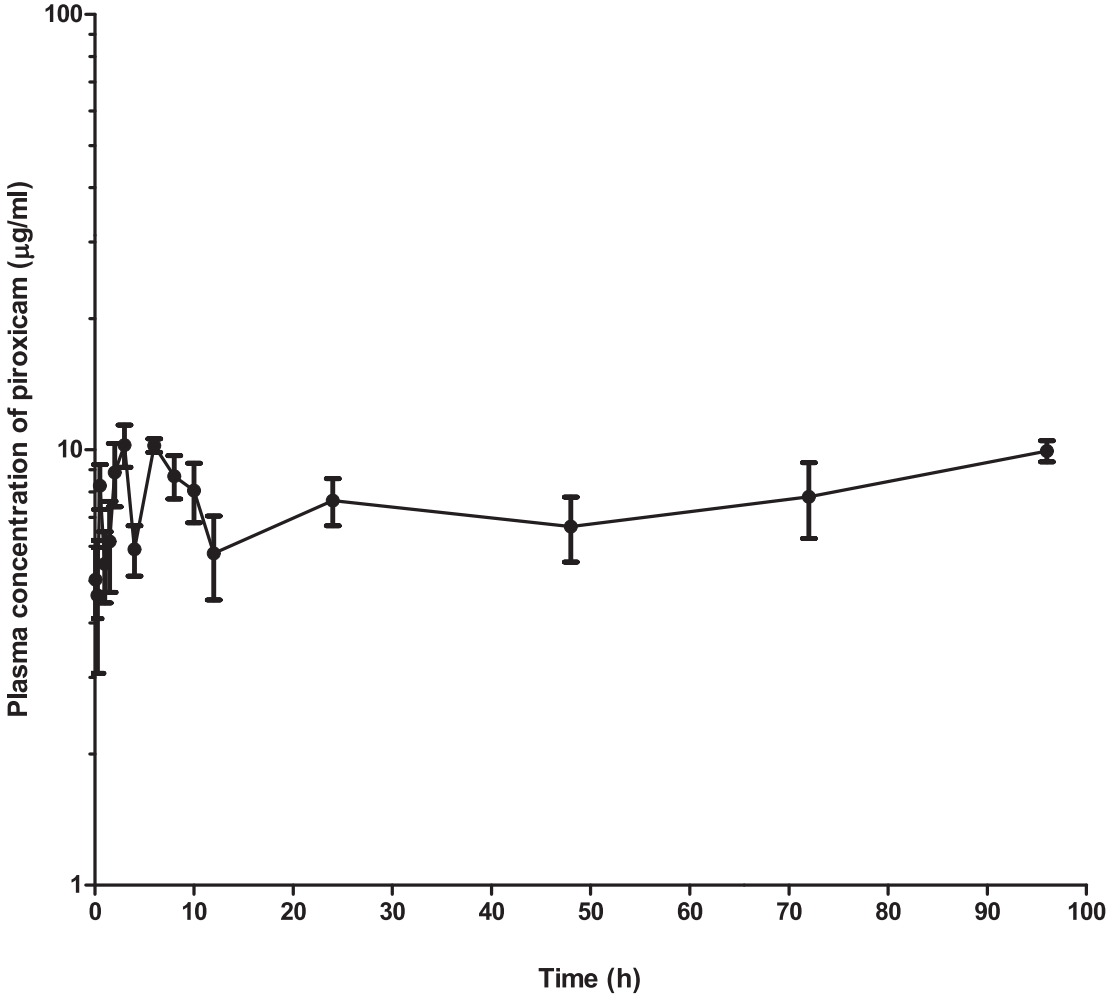

Fig. 2. Mean plasma concentration–time curve of 3.5 mg/kg intramuscular piroxicam coadministered with intramuscular diminazene aceturate (3.5 mg/kg) in dogs (n = 10).

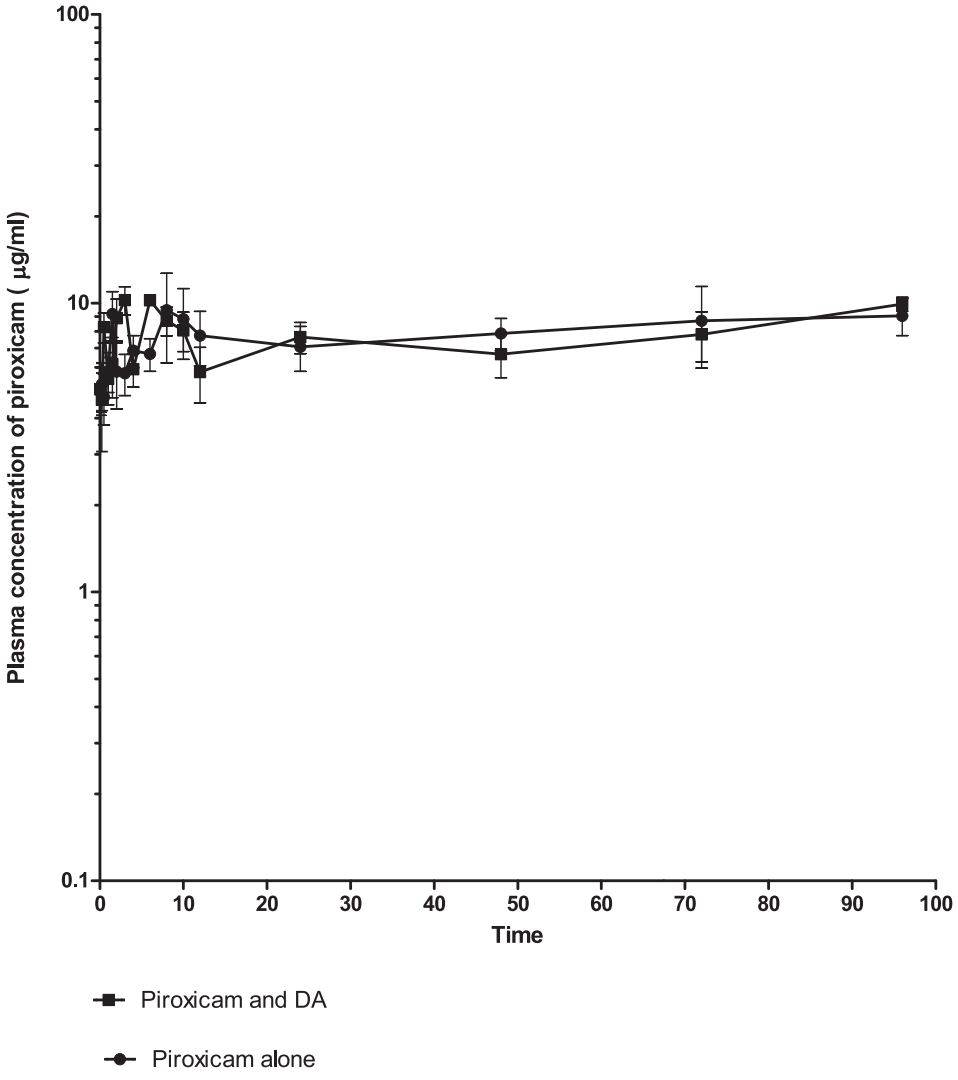

Fig. 3. Mean plasma concentration–time curve of 3.5 mg/kg intramuscular piroxicam, and 3.5 mg/kg of piroxicam/diminazene aceturate (3.5 mg/kg) in dogs respectively (n = 20).

Table 2
Pharmacokinetic parameters of piroxicam alone and piroxicam/diaminazene aceturate in dogs.

Kinetic parameters	Piroxicam alone	Diminazene aceturate/piroxicam
C_{max} (µ/ml)	18.560 ± 2.97	12.659 ± 0.85[b]
T_{max}(h)	45.000 ± 11.49	13.675 ± 9.21[b]
$\alpha(h^{-1})$	5.823 ± 1.46	7.405 ± 1.75[a]
$T_{1/2\alpha}$ (h)	0.250 ± 0.08	0.016 ± 0.04[b]
MAT(h)	0.361 ± 0.11	0.658 ± 0.45[a]
$\beta(h^{-1})$	0.935 ± 0.75	0.137 ± 0.10[b]
$T_{1/2\beta}$ (h)	33.634 ± 9.34	34.850 ± 11.94[a]
$AUC_{0\text{-}96}$(mg/L/h)	768.370 ± 9.34	734.832 ± 63.20[a]
$AUC_{0\text{-}\infty}$(mg/L/h)	814.472 ± 86.43	778.885 ± 66.99[b]
CL(L/kg/h)	0.0034 ± 0.00	0.003 ± 0.00
Vd(L/kg)	0.2062 ± 0.08	0.311 ± 0.16[a]
MRT(h)	49.793 ± 13.43	106.561 ± 54.84[a]
AUMC(mg/h^2/L)	36274.840 ± 9010.44	9820.140 ± 5.33[b]
$Fab_{0\text{-}96\ h\ (\%)}$	7.848 ± 0.00	7.505 ± 0.00[b]
$Fab_{(0\text{-}\infty\%)}$	8.319 ± 0.04	7.955 ± 0.03[b]
Faf(%)	–	95.63 ± 8.22

which drugs are diffused (Pintand et al., 1992). Reported is flip-flop kinetics of meclofenamic acid (horse), indomethacin (poultry), acetaminophen (rat) (Baggot, 2001), benzimidazole (horse), cefazolin (horse) (Baggot, 2001; Sams and Ruoff, 1985), amoxicillin/-clavulaninic acid (goat), amprolium (chicken) and sulphadimethoxine (ungulates), respectively (Baggot, 2001; Chatfield et al., 2001). Pathophysiological conditions that could cause flip-flop principle are congestive heart failure and liver cirrhosis (Brater et al., 1984; Fredrick et al., 1991). Different routes of drug administration could be responsible for flip-flop phenomenon (Yanaz et al., 2011). The decreased C_{max}, T_{max}, $T_{1/2\alpha}$, β, $AUC_{0\text{-}\infty}$ and AUMC as well as increased α, MAT, $AUC_{0\text{-}96h,}$Vd and MRT in the group administered piroxicam with diminazene aceturate are suggestive of non-linear mixed kinetics. Steady state concentration could yield optimal therapeutic regimen (Saganuwan, 2020), that maximum plasma concentration, maximum time reached, elimination half-life and volume of distribution are the most important kinetic parameters (Akogwu et al., 2017a,b, c). The disposition kinetics of piroxicam and piroxicam/diminazene aceturate in the present study disagrees with the report of Akogwu et al. (2017c) indicating that elimination of piroxicam in goats was independent of absorption. The higher elimination half-life (33.634 ± 9.34 h) of piroxicam and piroxicam/diminazene aceturate (34.85 ± 11.94 h) as compared to that of goat, mice, rat and rhesus monkey (2–9 h) show that piroxicam elimination is not absorption dependent in these species of animals (Akogwuet al., 2017a; Milone and Twomey, 1980). Elimination

half-life of 45 h has been reported for beagle (Hobbs and Twomey, 1981). The differences in species variation, route of administration and sex could be responsible for differences in the kinetic parameters. Therefore combination of the two drugs may be useful for the treatment of trypanosomosis, leishmniasis, amoebiasis, pneumocystis associated with fever, inflammation and pain (Oliveira and de Freitas, 2015).

Wagner-Nelson principle may be used to determine linear segment of absorption rate. Curved or curve linear segment of absorption may yield component of absorption rate over time (Wagner and Nelson, 1964). Hence a two compartment model could be collapsed into one compartment model. When absorption is first order in one compartment open model, but stops abruptly, Guggenhein method may be applied for calculation of absorption phase. Nevertheless, estimation error of elimination rate constant could lead to Wagner-Nelson absorbed fraction of kinetic greater than unity (Wang and Nedelman, 2002). Slow absorption rate of piroxicam may be due to low dose of piroxicam administered, invariably preventing side effects. High dose of administered piroxicam could be distributed faster than low doses (Saganuwan, 2016).

The slow release of piroxicam in dogs may be due to mechanochromic nature of the drug. Piroxicam is converted to zwitterionic compound via recrystallization and intermolecular proton transfer (Cheng and Choi, 2000). The breakdown of a weak C—O bond results in chemical change (Frank et al., 1996). Monohydrate form is more wettable, hence dissolves faster (Cini, et al., 2007) than other forms which are lypophilic (Saganuwan, 2016). Microencapsulated form has higher capacity of release in the plasma, as co-crystal formation with carboxylic acid increases its bioavailability (Vrecer et al., 2003). Cubic crystal better solubility and low extent of bioavailability (Liu et al., 2010), is related to protein binding capacity and sex difference (Akogwu et al., 2017a). High plasma level of piroxicam for long period correlates with its analgesic activity (Milone and Twomey, 1980). Piroxicam dissolved in polyvinylpypyrrolidine is highly viscous, hence released slowly (Takaca-Novak et al., 2004). Acidity of dog urine and enolic function of piroxicam with pKa of 2.68 (Christifis et al., 2005), may be responsible for its delay elimination. The acid-base property of piroxicam is responsible for its structure–activity relationship (Manewka et al., 2014). High piroxicam concentration decreases water molecule in the body, becoming apolar, that can result in concentration- independent high-energy shift of the absorption maximum (Shah, 2003). Hence dog administered piroxicam should be given large quantity of water for faster absorption and elimination. Piroxicam embedded in hydrophilic polymer may be released faster (Saganuwan, 2016). Addition of sodium or potassium to piroxicam enhances its pharmacokinetic and pharmacodynamic activity, and electrospinning increases dissolution rate (Lombardino and Lowe, 2004). A combined intramuscular formulation of piroxicam and diminazene aceturate of 3.5 mg/kg each could be a potent, high efficacious polypharmacy against trypanomosis and babesiosis. Many parenteral drugs are outside physiological pH range, hypertonic, and lack aqueous vehicles. Hence the absorption is erratic, causing tissue irritation and pain at the site of injection. Ampicillin, cephradine, dicloxacillin, quinidine, phenytoin and digoxin are not suitable for intramuscular injection. Propylene glycol cause drug precipitation at intramuscular injection site as seen with diazepam and phenytoin. Oily solution and aqueous suspension of drug are absorbed slowly as seen for ceftiofur (Baggot, 2001).

5. Conclusion

Piroxicam and piroxicam coadministered with diminazene aceturate showed flip-flop mechanism of absorption, invariably leading to long elimination half-life in dogs. Hence the combination may be good for the treatment of trypanosomosis, babesiosis, leishmaniasis, amoebiasis and pneumocytis in dogs. The combination therapy could be once or twice and be repeated when necessary.

Authors' contributions

SAS designed the study, did the statistical analysis and wrote the manuscript, OFE and AJO carried out the study, and all the authors proofread the manuscript.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2023.102914.

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