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EFFECT OF SODIUM BICARBONATE COADMINISTRATION ON THE PHARMACOKINETICS OF PIROXICAM IN HEALTHY ADULT MALE VOLUNTEERS

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Abstract

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties widely used for pain and inflammation associated to arthritis and infectious diseases. The aim of the study was to determine the effect of sodium bicarbonate coadministration on the pharmacokinetic profile of piroxicam in healthy adult male volunteers. Six (6) healthy adult male volunteers (age 23 ±5 years, weight 56 ± 5kg) were used for the study. A written consent was provided from each volunteer and ethical clearance for the study was similarly obtained from the Research and Innovation Directorate of Gombe State University, Nigeria. The UV spectrophotometric method adopted was validated by determination of linearity, precision, accuracy, percent recovery, limit of detection and limit of quantification. A calibration curve was constructed using five (5) piroxicam standards by plotting absorbance against concentrations of piroxicam. An in vivo study conducted involved two phases: phase I involved administration of piroxicam alone orally to the volunteers and phase II involved coadministration of piroxicam with sodium bicarbonate through the oral route. Urine samples were collected at different time intervals as follows: 0, 0.5, 1, 2, 4, 6, 12, 24 and 48 hours respectively. Consequently, urine concentrations of piroxicam were determined by uv spectrophotometric method. Values of the unknown piroxicam urine concentrations for each volunteer were determined by extrapolation of the standard curve. Pharmacokinetic parameters were obtained using kinetica 5.0 and SPSS PK Calculator and trapezoidal method. Data were presented as Mean ± Standard Deviation and analyzed using one-way analysis of variance (ANOVA). P values less than 0.05 were considered to be statistically significant. The results obtained indicated a calibration curve with linearity between 8 and 32 µg/mL and a correlation coefficient $r^2 = 0.987$. UV spectral analysis revealed 300 nm as the wavelength of maximum absorption of piroxicam. Percentage recovery was 97-100.3% which is within the accepted range of 95 - 105 %. Peak concentration of piroxicam increased significantly ($p < 0.05$) in piroxicam plus sodium bicarbonate group (32.3 ± 1.8 µg/mL) compared to piroxicam alone group. However, elimination half-life significantly ($p < 0.05$) decreased in piroxicam plus sodium bicarbonate group (51.63 ± 94.76 µg/mL) compared to control (98.1 ± 65.29 µg/mL). We can therefore conclude that, coadministration of piroxicam with sodium bicarbonate significantly ($p < 0.05$) increased the peak concentration (C_{max}) of piroxicam and decreased its elimination half-life ($t_{1/2}$) compared to piroxicam alone group.

Keywords: piroxicam, sodium bicarbonate, pharmacokinetics, urine samples, peak concentration

Introduction

The term pharmacokinetics was first introduced by Wagner (1981) in his book titled "Der blutspiegel". Pharmacokinetics is that branch of pharmacology that involves the change of one or more drug variables as a function of time. Pharmacokinetics is a branch of pharmacology concerned with the study and characterization of the time course of drug absorption, distribution, metabolism, excretion and the relationship of these processes to the intensity and time course of therapeutic and adverse effect of drugs (Gibaldi and Levy, 1976). According to Wagner (1981), the purpose of pharmacokinetics is to study the time course of drug and concentrations or amount of metabolites in biological fluids or tissues and to construct suitable models to interpret such data. According to Royal Pharmaceutical Society (2024), pharmacokinetics can be defined as the kinetics of absorption, distribution, metabolism and excretion (ADME). Sometimes, pharmacokinetics is described as what the body does to a drug – referring to the movement of drug into or through and out of the body (Le, 2024).

For a drug to have an effect, it must navigate at least one membrane except for intravenous or intra-arterial administered drugs. To enter general circulation from the site of administration, and in some cases to get to the site of action, a drug may need to overcome physical, chemical, or biologic barriers such as the blood–brain barrier (Golan *et al.,* 2012).

Pharmacokinetics is useful in selecting and adjusting drug dosage schedules and monitoring drug levels (therapeutic and toxic concentrations) in individuals. Pharmacokinetic parameters include area under the curve (AUC), maximum plasma concentration (C_{max}), time to attain maximum concentration (T_{max}), absorption half-life ($T_{½\alpha}$), absorption rate constant (K_α), elimination half-life ($t_{½\beta}$), elimination rate constant (K_β), Plasma clearance (Cl), volume of distribution (V_d) and lag time (Tripathi, 2018). The common routes of drug administration can be categorized as oral, topical, parenteral, and transdermal (Rang *et al.,* 2008). Oral route is the most common, simple, convenient, and painless route, allowing self-administration of drugs in easily handled forms. Orally administered drugs are absorbed from the gastrointestinal tract and transported via the portal system to the liver and may undergo first-pass metabolism. First-pass metabolism renders some of the drug molecules inactive, thereby decreasing bioavailability (Rang *et al.,* 2008). The absorption of a drug is dependent on many factors including the environment where the drug is absorbed, chemical characteristics of the drug, dosage form and route of administration, which influences bioavailability (Venkata *et al.,* 2019). Others are aqueous solubility, concentration, surface area of absorption and vascularity of absorbing surface (Tripathy 2019). Bioavailability refers to the rate and extent of absorption of a drug from a dosage form, irrespective of the route of administration, as determined by its concentration-time curve in blood or by its excretion in urine (Tripathy 2019). It is also a measure of the fraction of administered dose of a drug that reaches the systemic circulation in the unchanged form. Bioavailability of drug injected intravenously is 100%, but is decreased after oral ingestion because the drug may be incompletely absorbed in GIT or the

absorbed drug may undergo first pass metabolism in the intestinal wall/liver or be excreted in bile.

Drug absorption provides an avenue for drug interactions, be it positive or negative. Positive interaction could occur by increasing the absorption of another drug, whereas negative interaction occurs when absorption of a drug is greatly reduced by another drug (Katzung *et al*., 2004).

According to Naila *et al.*, (2018), piroxicam (PX) (4-hydroxy-2-methyl-3- (pyrid-2-yl-carbamoyl)-2H-1, 2-benzothiazine 1,1-dioxide) is a non-steroidal anti-inflammatory medicine (NSAID) that is the prototype of the oxicam class of drugs (Jennasari *et al.,* 2015). Because of their antipyretic, analgesic, and anti-inflammatory qualities, NSAIDs are among the most widely used medications worldwide (Pereira-Leite *et al.,* 2013). According to Ambrogi *et al.* (2007), they are frequently given for the treatment of acute musculoskeletal problems, osteoarthritis, and rheumatoid arthritis. Moreover, a study that involved repurposing drug delivery via topical route and repurposed drug in clinical trial have confirmed that piroxicam is a promising drug for the treatment of skin cancer (Kumber *et al.,* 2022) After being administered orally or rectal, piroxicam is easily absorbed. Typically, 20 mg of it is used daily. 99 percent of it is bound to plasma protein, has a long elimination half-life (35 to 60 hours), and is heavily metabolized into 5-hydroxypiroxicam (4-hydroxy-N-(5-hydroxy-2-pyridyl)-2-methyl-2H-1,2-benzothiazine-3-carboxamide) by CYP2C9 (isoenzymes of cytochrome P450) into 5-hydroxypiroxicam (4-hydroxy-N-(5-hydroxy-2-pyridyl)-2-methyl-2H-1,-2-benzothiazine-3-carboxamide 1, 1-dioxide) (Helmy and El-Bedaiwy 2014).

It is extensively metabolized by hepatic cytochrome P450 enzyme, principally to the hydroxyl metabolite. Hydroxylation occurs at the 5-position of the pyridyl ring and the hydroxylated metabolite undergoes subsequent glucuronidation. About 2–5% of an oral dose is excreted unchanged in urine, and, under steady state conditions, 75% of a dose is excreted either 5-hydroxypiroxicam (5-HP) or 5-hydroxypiroxicam glucuronide in urine and feces (Ambrogi *et al.,* 2007). After a single oral dose of 20 mg, peak plasma concentrations of piroxicam are of the order of 4.5 mg ml−1. No conjugates of piroxicam have been detected in plasma (Helmy and El-Bedaiwy 2014).

Serewinatne and colleagues (2024) emphasized that sodium bicarbonate is a multifaceted medication that plays a crucial role in managing and treating diverse pathologies. Because of its ability to cause metabolic acidosis, the Federal Drug Agency of the United States approved it use in severe renal disease, uncontrolled diabetes, severe primary lactic acidosis, circulatory insufficiency due to shock, severe dehydration, extracorporeal circulation of blood, cardiac arrest, drug toxicity, barbiturate intoxication, toxic alcohols, urine alkalinization and severe diarrhea with bicarbonate loss.

Materials and Methods

Methods

Sample collection

Piroxicam capsule 20 mg and ascorbic acid 100 mg were purchased from A. A. Aliyu Pharmacy in Gombe, Gombe State. They were stored in the fridge compartment set up at -4°C before time of use.

Blank urine samples

Fresh urine was collected in a plain sample bottle from a volunteer after undergoing an overnight fasting. It was then centrifuged at 600 rpm for 10 minutes and the supernatant layer decanted and finally stored in a refrigerator at -4˚C.

Analytical Method
Extraction of piroxicam.

Five (5) capsules of amount equivalent to 20 mg piroxicam was weighed and dissolved in 50 mL methanol. The solvent was allowed to evaporate overnight and the powder was recovered.

Preparation of stock solution

Stock solution of piroxicam was prepared by dissolving 10 mg of accurately weighed piroxicam standard powder in 20 mL methanol solution contained in 100 mL volumetric flask and making up to volume with the same solvent to obtained 100 µg/mL stock solution.

Determination of wavelength of maximum absorption

One milliliter (1 mL) of the stock solution prepared above was withdrawn and transferred into a volumetric flask and made up to 10 mL with methanol to obtain 10 µg/mL solution. This was then scanned through a wavelength range of 200-400 nm to determine the wavelength of maximum absorption.

Preparation of calibration curve

Five-point calibration curve was constructed by spiking 0.5 mL blank urine supernatant contained in five (5) labeled test tubes with 0.2, 0.4, 0.8, 1.6 and 3.2 µg/mL stock solution of piroxicam as standard. The mixture was then made up to volume with methanol solution in the 10 mL test tubes. Absorbance is recorded at the scanned maximum wavelength of absorption. The absorbance obtained were plotted against the spiked standard concentrations.

Validation of the developed analytical method

The developed method was validated for its linearity, precision, accuracy or percentage recovery, limit of detection (LOD), and limit of quantification (LOQ) according to International Conference on Harmonization (ICH) guideline 1995.

Linearity

The linearity of this developed method was established by least square using Microsoft Excel 2007.

Intra-day precision

Concentrations of 16 and 32 µg/mL solutions of piroxicam respectively were used for the within-day precision. Their absorbance was measured hourly at 300 nm for up to three (3) times in order to get six (6) determinations. Their means, standard deviations and relative standard deviations (RSD %) were then calculated.

Inter-day precision
This consists of measuring the absorbance of the 32 µg/mL solution in triplicate for three (3) consecutive days in order to get nine (9) determinations. The mean, standard deviation and relative standard deviation (RSD %) were calculated.

Percentage recovery / Accuracy

Accuracy of the analytical method was determined by recovery study where 4, 6

and 8 µg/mL of standard drug were added respectively to three (3) different test tubes each containing the stock solution left un-spiked. The absorbance was then measured and the percentage recovery was calculated as follows:

% Recovery = $\frac{Observed\ concentration}{Expected\ concentration}$ X 100

Limit of Detection

The limit of detection (LOD) may be expressed as:

$$LOD = \frac{3.3*\sigma}{S}$$

Where σ = the standard deviation of the response,

S = the slope of the calibration graph

Limit of Quantification

The quantification limit (QL) may be expressed as:

$$QL = 10 * a/S$$

Where σ = the standard deviation of the response,

S = the slope of the calibration graph

In-vivo Pharmacokinetic Studies of Piroxicam and Sodium Bicarbonate

Study protocol

Six (6) healthy adult male volunteers (aged 23 ± 5 years, weight 55 ± 5 kg) were used for the study. Exclusion criteria for the study include smoking, alcoholism, liver and kidney dysfunction and hypersensitivity to piroxicam. Ethical approval was sought from Gombe State University Ethical Committee for the Use of Human Subjects in Research. Also, consent was obtained from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. All volunteers were instructed to abstain from drugs or any herbal medicines two weeks before the commencement of the study.

Study design

This study contained two (2) phases in which the drugs were administered to the volunteers after an overnight fasting and a washout period of two (2) weeks between the two phases.

Drug administration and collection of urine samples

Phase I (Piroxicam alone): After single oral administration of 20 mg piroxicam capsule with a glass of water, urine samples were collected from each of the six (6) healthy male volunteers at different time intervals: 0, 0.5, 1, 2, 4, 6, 12, 24, and 48 hours respectively. Piroxicam and metabolite were extracted from the urine samples using methanol, centrifuged, and 0.5 mL the supernatant obtained was removed and stored at -4 °C before analysis.

Phase II (Piroxicam plus sodium bicarbonate): Following a concurrent administration of 20 mg piroxicam with two tablets of 300 mg of sodium bicarbonate, urine samples at volume of 0.5 mL were collected into plain sample bottles from each of the six (6) healthy male volunteers at time 0, 0.5, 1, 2, 4, 6, 12, 24, and 48 hours. Piroxicam and metabolite were extracted from the urine samples using methanol, centrifuged, and 0.5 mL the supernatant obtained was collected and stored at -4 °C before analysis.

The concentrations of the unknown samples for control and tests were determined by extrapolation of the calibration curve of piroxicam standard. Pharmacokinetic parameters were generated using the Microsoft excel 2007 software and SPSS/PK calculator.

Statistical Analysis

Results were expressed as Mean ± Standard Deviation and statistical analysis were conducted using students' paired *t*-test at 95 % confidence interval, p values less than 0.05 were considered to be statistically significant.

Results

Construction of Calibration Curve

Result obtained indicated a relative correlation coefficient of 0.9872 after plotting known concentrations of piroxicam standard against their corresponding absorbance as shown in Figure 1 below:

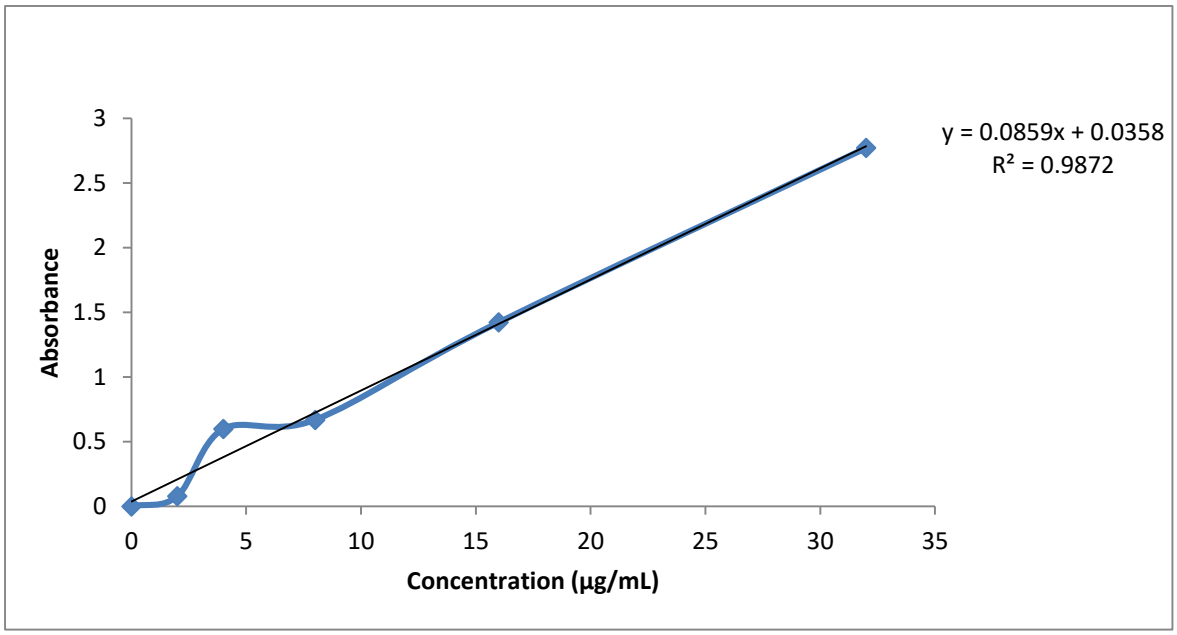

Figure 1: Calibration curve of piroxicam standard in urine at 300 nm

Validation of the Analytical Method

Precision of the analytical method

The intra-day and inter-day precisions were found to be < 2 % as indicated by their percentage RSD (Tables 1 and 2)

Table 1: Within-day Precision Using 16 and 32 µg/mL Piroxicam Solution

Concentration	Mean ± SD	% RSD
16	1.426 ± 0.00057	0.03997
32	2.775 ± 0.0031	0.1117

Table 2: Inter-day Precision Using 32 µg/mL Piroxicam Solution

Day	Mean ± SD	RSD (%)
1	2.775 ± 0.0031	0.1117
2	2.789 ± 0.0062	0.2223
3	2.893 ± 0.0021	0.0726

Accuracy and percentage recovery of the analytical method

The percentage recovery was found to be between the acceptable limit of 95-105% (Table 3)

Table 3: Percentage Recovery of Piroxicam Powder Spiked in Urine

S/N	Amount added (µg/mL)	Amount found (µg/mL)	Percentage recovery (%)
1	4	4.011	100.27
2	6	13.164	219.4
3	8	7.8	97.5

Limit of quantification (LOQ) and limit of detection (LOD) of the developed method were 121.05 and 0.95 respectively as show in Table 4 below:

Table 4: Limit of Quantification and Limit of Detection of the Developed Method

S/No	Parameter	Result Obtained
1	Limit of Quantification	121.05µg/mL
2	Limit of Detection	0.95µg/mL

***In-vivo* Studies**

The mean piroxicam concentration of combination group increased significantly and maximally after 4 hours (30.42 ± 3.76 µg/mL) and 6 hours (31.23 ±3.02 µg/mL) compared to control values (17.82 ± 11.24 µg/mL; 21.96 ± 7.21 µg/mL) respectively as shown in Table 5. The slope of piroxicam combined with sodium bicarbonate was steeper at the elimination phase compared to piroxicam alone control group (Figure 2).

Table 5: Mean Urine Concentrations of Piroxicam (µg/mL) in Piroxicam Alone and Piroxicam Plus Sodium Bicarbonate Group

Time (Hours)	Piroxicam Alone (Mean ± SD)	Piroxicam + Sodium Bicarbonate (Mean ± SD)
0.5	8.53 ± 10.64	16.09 ± 10.76
1	12.95 ± 10.40	22.59 ± 9.29
2	16.76 ± 11.10	25.64 ± 8.43
4	17.82 ± 11.24	30.42 ± 3.76*
6	21.96 ± 7.21	31.23 ± 3.02*
12	28.00 ± 4.57	28.8 ± 0.77
24	21.89 ± 6.86	23.82 ± 3.90
48	18.16 ± 9.80	12.96 ± 6.84

Data was analyzed using student's paired t-test; n = 6; * = Difference between means is statistically significant at < 0.05

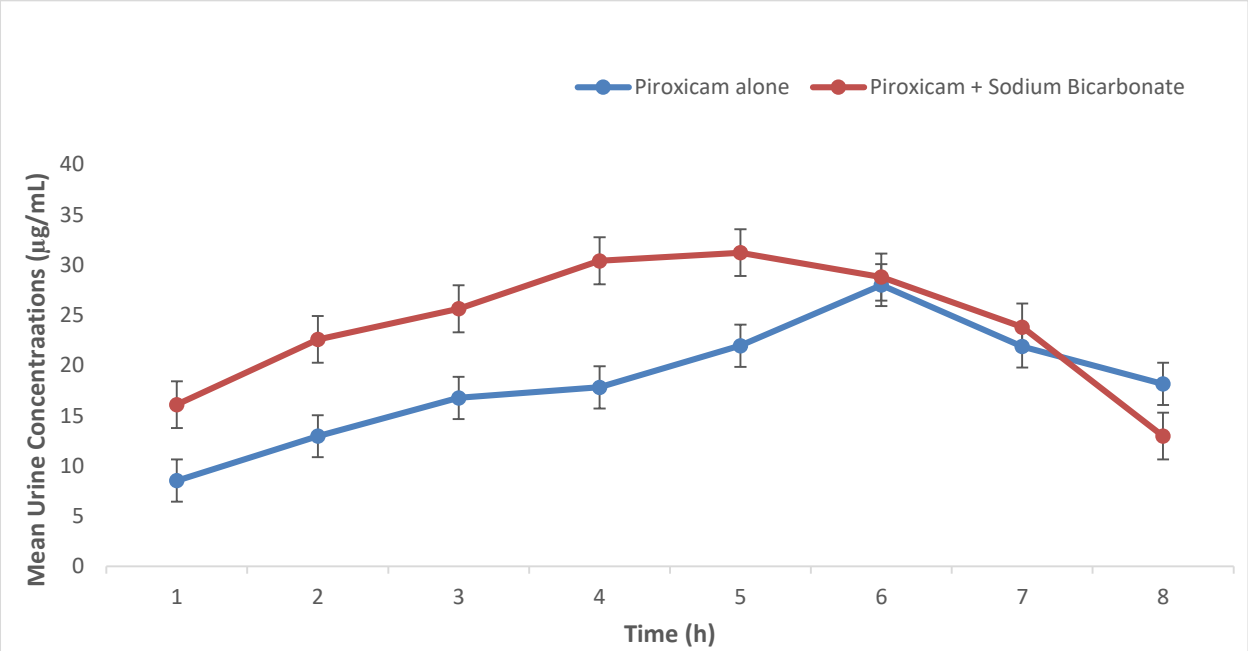

Figure 2: Urine concentrations of piroxicam alone and in combination with sodium bicarbonate in healthy male volunteers

Individual pharmacokinetic profile superimposed on one graph for piroxicam alone group was plotted and presented in figure 3. All phases of drug disposition for subjects 2-4 were almost similar. While subject 1 had a wider distribution phase subject 6 had a prolonged elimination phase.

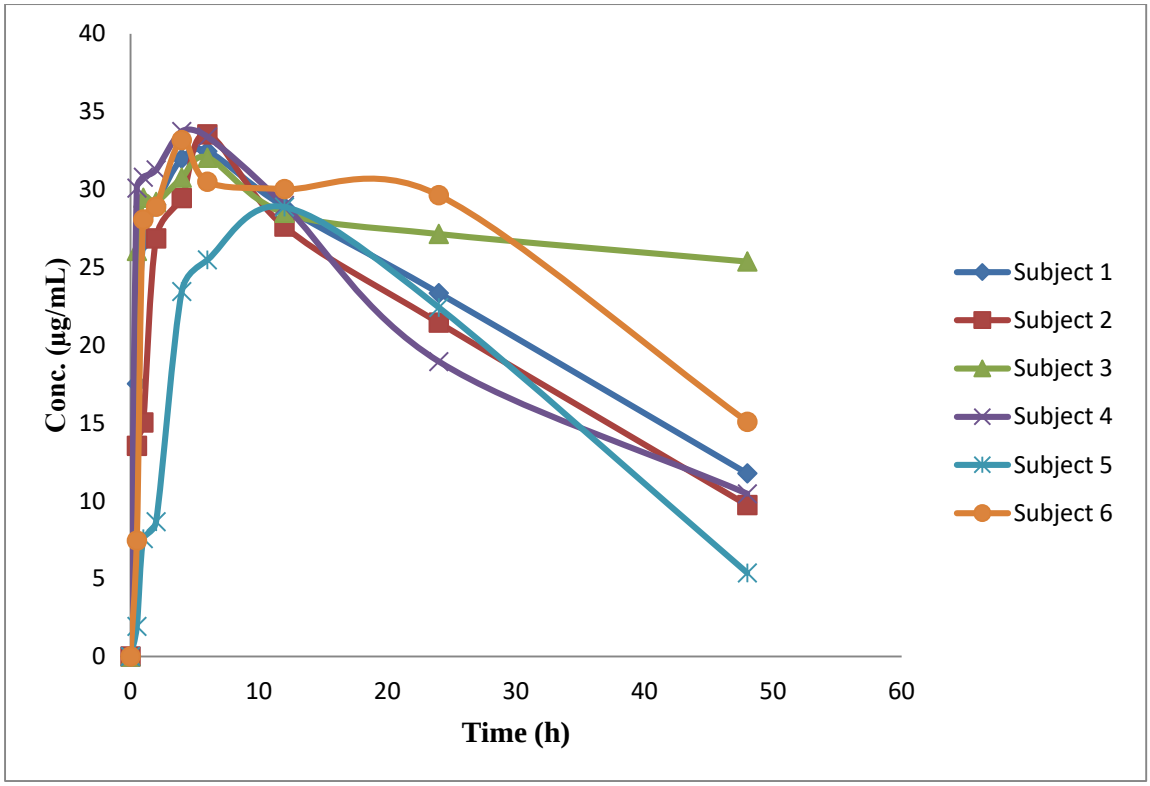

Figure 3: Individual urine concentration-time profile of piroxicam alone of six healthy male volunteers

After administration of sodium bicarbonate the distribution and elimination of piroxicam decreased in subject 1. However, the slope of all other subjects became gentle, indicating a delay in elimination of piroxicam (Figure 4).

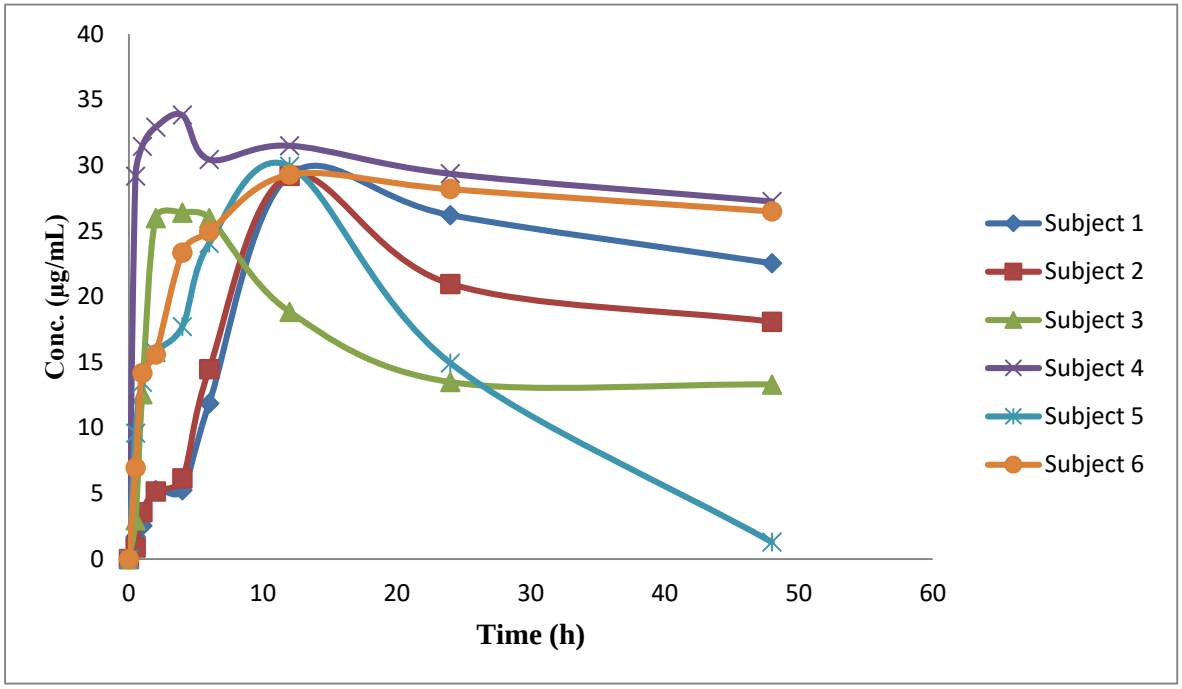

Figure 4: Individual urine concentration-time profile of piroxicam coadministered with sodium bicarbonate of six healthy adult male volunteers

Pharmacokinetic parameters

Mean ± Standard Error of Mean pharmacokinetics parameters of piroxicam derived using SPSS calculator and analyzed using student's t-test were presented in table 6 below. The result indicated a significant ($p < 0.05$) decrease in elimination half-life (t1/2) of 51 ± 94.76 h in piroxicam co-administered with sodium bicarbonate group compared with piroxicam alone group 98 ± 65.29 h. Conversely, peak concentration (Cmax) significantly increased in test group (32.3 ± 1.80* µg/mL) compared to control group (29.6 ± 2.39 µg/mL).

Table 6: Pharmacokinetic Parameters of Healthy Human Volunteers in the Two Phases

Parameter	Piroxicam Alone	Piroxicam + Sodium Bicarbonate
T½ (Hours)	98.1 ± 65.29	51.63 ± 94.76*
AUC $_{0-48}$	927.2 ± 308.35	1115.5 ± 190.59
AUC $_{0-\alpha}$	4087.1 ± 2793.67	3880.4 ± 3977.49
K_e (h^{-1})	0.0084	0.0063
Vd (l)	6.8	6.1
% Extrap	62.9 ± 31.73	43.8 ± 32.59
C_{max} (µg/mL)	29.6 ± 2.39	32.3 ± 1.80*
T_{max} (h)	9.3 ± 4.13	6.3 ± 2.94

Data was analyzed using student's paired t-test; n = 6; * = Difference between means is statistically significant at $p < 0.05$

Discussion

A correlation coefficient of 0.9872 shows a linear relationship between concentration of standard piroxicam and their corresponding absorbance. The calibration curve had obeyed Beer Lambert's law with a linearity range of 10-35 µg/mL. Abed and Hadi (2020) reported a linearity of piroxicam of a range of 1-35 µg/mL. Similarly, the limit of quantification of 121.05 µg/mL accommodates all the concentrations obtained *in vitro* and *in vivo*. In addition a limit of detection of 0.95 µg/mL indicate that the spectrophotometer used could detect and quantify all chromophers within the ultraviolent range which could be lower or higher concentrations of drugs in the plasma. Both piroxicam alone and piroxicam coadministered with sodium bicarbonate test group shows a hyperbolic profile indicating the appearance of absorption, distribution, metabolism and excretion phases. The peak concentration was significantly increased by sodium bicarbonate because it increases ionization of piroxicam thereby reducing its absorption from the stomach. Hobbs (1983) reported a peak concentration of about 2 ug/mL after a single oral dose of 20 mg in man and a concentration at steady state of 6 µg/mL. Urine excretion

of piroxicam is increased since sodium bicarbonate alkalinizes the urine. Also, its rate and extent of absorption is favored by a larger absorption surface area on reaching the intestine despite the number of ionic species present. Peak plasma concentration of a drug refers to the highest concentration of a drug in bloodstream after administration, which is crucial for evaluating its safety and effectiveness. Although this did not change the area under the curve, AUC significantly ($p < 0.05$) But there was a slight increase. Urine concentrations of piroxicam are correlated well with that in plasma since passive tubular reabsorption of piroxicam occur in the distal tubule maintaining its concentration in blood. Report indicated that the metabolite of piroxicam, 5-hydroxypyroxicam, is equally active and had been quantified spectrophotometrically (Verbeek, *et al.*, 1986). The elimination half-life of piroxicam significantly decreased due to a decrease in elimination rate constant and possibly total clearance. Bannwart, and coworkers (2001) reported a plasma half-life of 90.7 hours in synovial fluid.

In conclusion, it can be suggested that coadministration of piroxicam with sodium bicarbonate significantly ($p < 0.05$) increased the peak concentration (C_{max}) of piroxicam. But its elimination half-life ($t_{1/2}$) was significantly decreased compared to piroxicam alone group.

Declaration of Interest, Funding and Acknowledgements

There was no conflict of interest whatsoever as to the conduct of this study either with regards to funding, ethics or administration. The study did not receive any special grant institutional or otherwise. It was funded by self from monthly earnings as an academic staff and supported by other coauthors listed initially.

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