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EFFECT OF COCONUT (*COSCOS NUCIFERA L.*) WATER ON THE PHARMACOKINETIC PARAMETERS OF IBUPROFEN IN RABBITS.

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ABSTRACTS

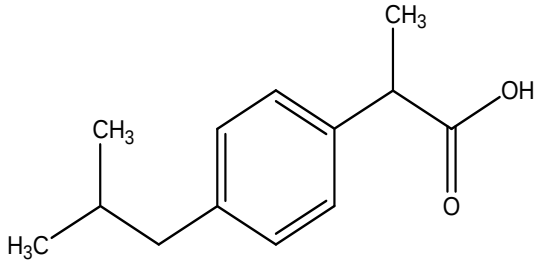
To evaluate the effect of pre and post administration of coconut water on the pharmacokinetic parameters of single dose ibuprofen (2.5kg/kg body weight) in rabbits. A total of nine male and female rabbits were used in this study. The single dose pharmacokinetics of ibuprofen (2.5kg/kg body weight) was evaluated before and after 30minutes of coconut water administration. Plasma ibuprofen concentrations were determined using precise, reversed-phase HPLC protocol. Model independent methods were used to evaluate the pharmacokinetics of ibuprofen. Data were analyzed by 2 way ANOVA testing followed by students' t-test. The relative bioavailability was observed to be 62.149% and 69.250%. The result showed that there was a significant reduction in the bioavailability of the study group II and I when compared with the control group. It was also observed that the mean plasma concentration (C_{max}) for the study group I and II (30minutes pre and post administration of coconut water) was found to be 12.3±1.20 and 14.3±1.40 respectively compared to the C_{max} value of 17.9±1.60 for the control group with ibuprofen alone. This difference was considered quite significant when compared with those of the control group with ibuprofen alone administered ($P < 0.05$). The area under the mean plasma concentration versus time curve ($AUC_{t\text{-}12}$) for the study group I and II was observed to be 3158.4 and 3591.3 µg/hr/ml respectively when compared to those of the control group (5082.0). there was a remarkable significant difference between the observed $AUC_{1\text{-}12hr}$ for the different study groups when compared with the standard but there was no significant increase in T_{max} amongst the various groups when compared to those of the control, the T_{max} were found to be 1.5±0.02 and 1.5±0.01 respectively for study groups I, II and control. The HPLC method adapted was validated by using various methods of validation parameters.

KEYWORDS: Ibuprofen, bioavailability, plasma, pharmacokinetics.

INTRODUCTION

In recent times drug toxicity and adverse drug reaction due to overdose has posed a lot of concern to the clinicians at large. The number of death due to drug toxicity and adverse drug reaction is estimated to rise far above an average of 120 per day in the United States of America.[1] Demographical distribution among the various age groups shows that children are more affected than adults though toxicity due to overdose is on the increase among the geriatrics. The use of herbal medicine in the management of adverse drug reaction and drug toxicity due to overdose has received greater attention amongst the Chinese[2,4] and Indian traditional medical practice. In West African region of Cameroon, Nigeria, Ghana and the Gambia, the indigenes have used palm oil, charcoal, palm kernel oil as well as coconut water in the management of drug poisoning and adverse drug reaction. Coconut trees are known to grow freely on the coastal region of West Africa and Asia. The nut is used for food while the oil and coconut water are used in ethno medicine for memory loss, impotence and antidote for poisons. To study drug – drug or drug – herbal medicine interaction, a complete knowledge of the pharmacokinetic parameter as well as the effect of drug on the bioavailability of the second interacting agent must be established.[5] Ibuprofen is an anti-inflammatory agent (NSAID) used as an analgesic drug and to reduce inflammation associated with many disease condition such as osteoarthritis[6], rheumatoid arthritis[7] and postoperative pains.[8] The mechanism of action of ibuprofen resides in its ability to inhibit the cyclo-oxygenase enzyme pathway thereby reducing the synthesis of prostaglandings.[9] Ibuprofen has two racimic mixtures: (+) S- and (-) R – enantiomeric forms.[10] This research investigates the effect of pre and post administration of coco-nut water on the Pharmacokinetic parameters of ibuprofen in rabbits.

Structure of ibuprofen



Sample collection

Ten fresh nuts of Coconut (*Cocos nucifera)* were purchased in the month of July 2017 from Choba market, Port Harcourt, Rivers State, South – south. Nigeria and these nuts were subsequently used for the experiment.

Experimental protocol

All animal study protocol was carried out in accordance with the guidelines of the Committee on Care and Use of Experimental Animals and Environmental Ethics, University of Port Harcourt. Nine male and female rabbits of both sexes (2.5 – 3.0 kg) obtained from the animal house of University of Port Harcourt, Nigeria were housed in three groups of three each, in a 12 hour light/dark cycle at room temperature and were fasted for 24 hours with free access to water before the experiment. The animals were randomly divided into three groups of three each. Group 1 received 50 ml of coconut water 30 minutes before 2.5 mg/kg body weight ibuprofen suspension each. Group II received 2.5 mg/kg body weight ibuprofen 30 minutes after 50 ml of coconut water, while group III received only 2.5 mg/kg body weight ibuprofen (control). The drug suspension was given by oral intubation. Blood samples (0.5ml) were collected at intervals of 0, 0.5,1, 1.5, 2, 2.5, 3,4,10 and 12 hours respectively via a modified needle cannula in the animal ear lobe vein. Samples were placed in the collection tubes containing heparin. The blood sample was centrifuged at 3,000rpm for 10minutes and the plasma obtained was stored at -20^{o}C until use.

Extraction

The frozen plasma was thawed at room temperature just prior to extraction. The plasma protein in the plasma was precipitated using acetonitrile[11] by mixing carefully for 10minutes. After centrifuging at 3,000rpm for 10minutes, the acetonitrile layer was re-extracted in 2.0ml of chloroform, mixed for 5minutes and evaporated to dryness.

Sample preparation

The drug sample was reconstituted in 2.0ml of analytical methanol. The resultant solution was transferred to HPLC injection vials and injected into the HPLC system at a volume of 50µL.

2.6 HPLC ASSAY

The HPLC system featured a Hitachi Lachrom Elite HPLC and auto-sampler in hyphenation to a UV-Vis spectrophotometer set at 214nm. Degassed mobile phase consisting of methanol:Acetonitrile:Phosphate buffer (45:45:10) was pumped through the column at a flow rate of 1.0ml/min. Ibuprofen and the internal standard (diclofenac) were monitored at 214nm wavelength. The compounds were separated on Genesis C_{18} column (0.46 x15cm, 3μm). Drug standard curves were constructed for ibuprofen between the concentrations of 5 and 200 μg/ml. The operation was carried out under room temperature.

Preparation of standard solution for calibration

To 1mg of standard ibuprofen was added 5ml of methanol to afford 200µg/ml, 1ml was taken from the stock solution (200µg/ml) into a 10ml volumetric flask and the volume made up to mark to get 20µg/ml. 5ml of the 20 µg/ml stock solution were taken into 10ml volumetric flask and also made up to volume with methanol to afford 5µg/ml. The above concentrations were used to obtain the calibration plot (Peak area against concentration).

DATA ANALYSIS

Data from plasma concentration time curve within 12 hours after drug administration were used to estimate the necessary pharmacokinetic parameter for the individual rabbit in each groups including peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the sigma plot 11 software was employed in the computation of area under the plasma concentration versus time curve from zero to last sampling time ($AUC_{0\text{-}12hr}$). Student's t-test was performed to evaluate the significant differences between the three variables. Values were reported as mean $\pm$SD and the data were considered statistically significant at $p<0.05$. The percent bioavailability (F) was calculated from the following formula:

$$F\ (\%) = \frac{AUCtest}{AUCstandard}\ x\ 100 \qquad \text{equation .....1}$$

The elimination rate constant (K) was calculated from graphical representation of equation 2 using the line of best fit of four points in the elimination phase:

$$Cp = Cpo^{-ekt} \qquad \text{equation.....2}$$

Where Cp and Cpo are plasma concentration of ibuprofen at time t and t = 0. Ibuprofen half life ($t_{1/2}$) was obtained from equation 3

$t_{1/2} = 0.693/K$ equation 3

Peak plasma concentration (Cmax) and time for peak plasma concentration (t_{max}) were estimated from the plasma level-time curves.

RESULTS

Calibration plot

The linearity obtained from the peak area versus plasma concentration of reference ibuprofen indicates that the Beer's law was obeyed. The calibration curve for ibuprofen was linear over the range of 5 – 200 µg/ml (Figure 2).

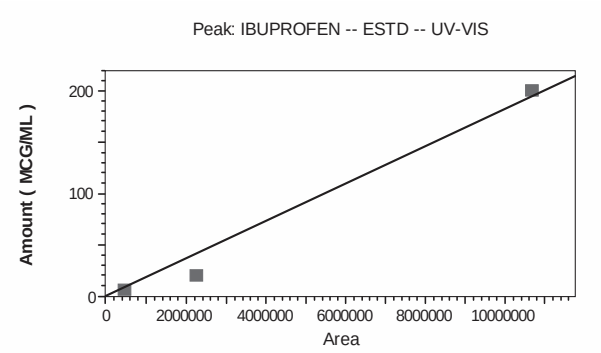


Figure 2: Calibration curve for Ibuprofen.

The Chromatogram of both the internal and external standard (Ibuprofen and Diclofenac) gave an observed retention time of 3.937 and 4.262 minutes respectively when spiked (Figure 3).

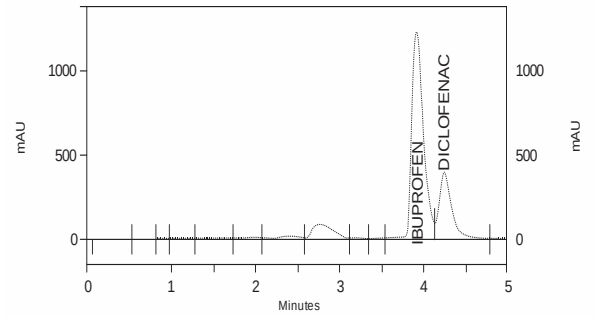


Figure 3: Chromatogram of Ibuprofen and Diclofenac.

Pharmacokinetic parameters of Ibuprofen in the absence and presence of Coconut water, administered 30 minutes (Pre and post administration) are shown in Table 1. While the Plasma concentration – Time profile are shown in figure 4. In all cases, Ibuprofen was rapidly absorbed with a mean t_{max} of 1.5 hours in all the study groups investigated. The plasma concentration – time curves of Ibuprofen in all the study groups investigated showed a correlated decline in distribution and elimination phases (Figure 4). The mean values of Cmax, AUC_{0-12} and $AUC_{0-\alpha}$ for Ibuprofen were significantly reduced ($P < 0.05$) when Ibuprofen was given 30 minutes pre and post administration of Coconut water when compared to those of Ibuprofen alone (control). The values for the above stated parameters are shown in table 1 respectively. The overall effect was the reduction in the bioavailability of Ibuprofen administered 30 minutes (Pre and post administration of Coconut water) There was a remarkable reduction in the peak plasma (Cmax) concentration of Ibuprofen, however, the time taken to attain peak plasma concentration (t_{max}) were not affected by the administration of Coconut water. There was also no significant difference amongst the observed half life ($t_{1/2}$) for the various study groups.

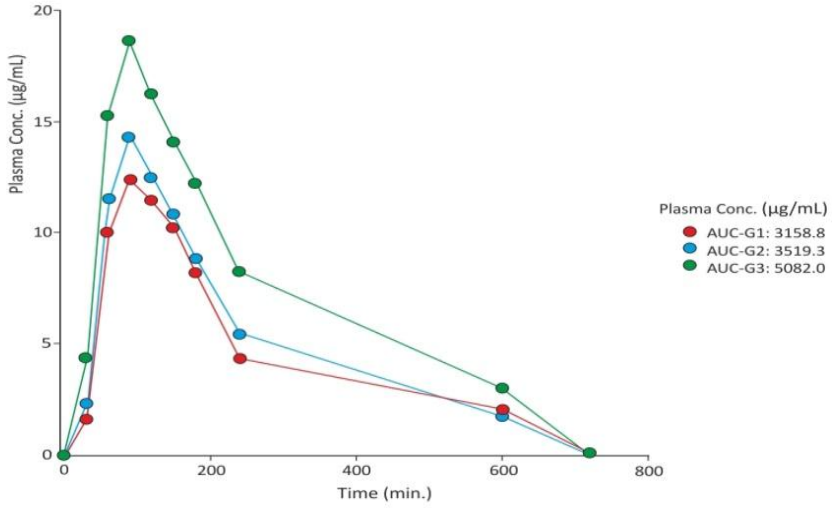


Figure 4: Plasma level – time curves of ibuprofen administered in the presence and absence of coconut water.

Table 1: Important Pharmacokinetic parameters of Ibuprofen (2.5 mg/kg) given 30 minutes before Coconut water, 30 minutes after Coconut water (cw) and Ibuprofen alone.

Parameters and unit	Ibuprofen (n=9)		
	30 min before coconut water group 1	30 min after coconut water group 2	2.5 mg/kg (Ibuprofen alone) Group 3
AUC_{0-12} (µg/h/ml)	3158.4	3591.3	5082.0
$AUC_{0-\alpha}$ (µg/h/ml)	3160.1	3598.6	5088.4
Cmax (µg/ml)	12.3±1.20	14.3±1.40	17.9±1.60
$t_{max\ (h)}$	1.5±0.02	1.5±0.01	1.5±0.02
$t_{½\ \ (h)}$	0.6±0.05	0.6±0.02	0.8±0.01
K (hr^{-1})	1.155.	1.155	0.866
F (%)	62.149	69.250	100

DISCUSSION

Literature review shows that little or no documentation is available on the effect of coconut water on the extent of absorption of Ibuprofen in animals. It is evident from this research that the presence of coconut water delayed the rate of absorption of Ibuprofen resulting in a reduction in the observed Cmax, AUC_{0-12hr} and invariably the bioavailability of Ibuprofen. This observed reduction of some vital pharmacokinetic parameters could be as a result of interaction (absorption interaction) between coconut water and Ibuprofen.[12] Other postulation could be due to reduction in gastric motility caused by some phytochemicals in the coconut water such as the essential lipids and stabilizing proteins which may have delayed gastric emptying.[13,15] The mean plasma concentration was reduced from 17.9±1.6 µg/ml to 12.3±1.2 and 14.3±1.4 µg/ml in the two study groups respectively, this reduction is quite significant and one can ascertain that coconut water had a remarkable effect on the pharmacokinetic parameters of Ibuprofen and this could justify the ethno medicinal uses of coconut water by the local African populace in the management of drug poisoning and over dose.

CONCLUSION

In the reported research work, the pharmacokinetic parameters of Ibuprofen were well affected in the presence of Coconut water. Patients on drugs especially Ibuprofen are advised not to take their medication with Coconut water or Coconut water based supplements, but in time of accidental Ibuprofen overdose, Coconut water (quantity sufficient) could be recommended.

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Conflict of interest

The authors report no conflict of interest.

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