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CHANGES IN THE PHARMACOKINETICS OF PIROXICAM IN DEHYDRATED RABBITS

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The study was aimed to investigate the effect of dehydration on the pharmacokinetic parameters of piroxicam in rabbits. The high performance liquid chromatographic method was employed for determination of piroxicam in plasma. All the pharmacokinetic parameters except Cl_T and Vd were observed to be decreased significantly ($p<0.01$) in the case of dehydration. The results reflect very well that water deprivation has a profound effect leading to change in the bioavailability and disposition kinetics of piroxicam which suggests an adjustment of dosage regimen in clinical conditions.

Keywords: *Piroxicam; Pharmacokinetics; Bioavailability; Feldene; Dehydration; Anti-inflammatory drug*

Introduction

Dehydration is an excessive loss of biofluids from body in which the body water contents become below the standard amounts. The most prominent manifestations due to water deprivation are loss of body weight and decrease of both blood and plasma volumes (1). In this condition, the plasma osmotic pressure, plasma protein concentration and hematocrit values increases but the pH and acid-base status of the blood remains unaffected (2-5). Dehydration has the potential of changing various physiological and biochemical parameters which may significantly modify the bioavailability and disposition of drugs. The changes in drug disposition kinetics may result in altered sensitivity and toxicity of drugs requiring a new basis of drug selection and dosage modification. In the present study, the influence of dehydration on the pharmacokinetic behavior of piroxicam was studied.

Materials and Methods

Animals

A total number of 9 healthy rabbits of either sex ranging in body weight from 1.3-2.6 kg were used. All the animals were maintained under similar conditions. The animals were fed with fresh green fodder and black gram in the morning and evening while the water was provided *ad-libitum*.

Plan of study

Pharmacokinetics of piroxicam was studied after administration of an oral dose in normal and dehydrated rabbits. The dehydration condition was produced in the normal animals after giving a wash out period of at least 10 days.

Induction of dehydration

Dehydration was produced by keeping the rabbits off water but not food. Body weight of the animals was recorded daily. The animals with a significant decrease in total protein level, packed cell volume and body weight were declared dehydrated (6).

Drug administration

The contents of Feldene capsules (10 mg/20 mg of piroxicam) (Pfizer Laboratories Pvt. Ltd. Karachi-Pakistan) was suspended in distilled water. The amount of the prepared suspension was calculated and administered orally through a feeding needle fixed on a 10 ml syringe, at a dosage rate of 5 mg/kg body weight.

Sampling procedure

Three ml of blood samples were drawn from the jugular vein of the rabbits and were collected in the heparinized centrifuge tubes just before

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and at 0.5, 1.0, 1.5, 2.5, 4.0, 6.0, 8.0 and 12.0 hours following the drug administration. The blood samples were centrifuged at 3000 to 4000 rpm for 10 minutes. Plasma was separated and used for the analysis.

Estimation of Piroxicam

High performance liquid chromatographic method developed by Tsai et al., (7) was followed in this study after some modifications. A 0.5 ml aliquot of plasma was pipetted into a 15 ml glass stoppered centrifuge tube along with 1 ml of Sorensens citrate buffer (pH 3). The mixture was shaken for 10 seconds and extracted with 5 ml of ethyl ether by mechanical shaking for 20 minutes. After centrifugation for 3 minutes at 3000 rpm, 4 ml of the organic layer was transferred to another tube and evaporated to dryness on a water bath at 50°C. The residue was reconstituted in 1 ml of mobile phase in which, 1 ml of indomethacin was added as an internal standard at a concentration of 50 µg/ml and mixed for 15 seconds by a vortex mixer. 20 µl of this solution was injected into the column of HPLC by means of graduated microsyringe (Hamilton, USA).

The HPLC system consisted of an injection valve (Rheodyne, USA), fitted with an injection loop of 20 µl capacity and a multi wave lenght detector UV (SPD-6 AV, Shimadzu, Japan), having absorbance of 0.001-2.56 aufs, and solvent metering pumps working at about 200 kgf/cm^2 pressure (LC-9 A, Shimadzu, Japan). The chromatographic separation was achieved on a reverse phase ODS-C18 column (15 cm x 4.6 mm i.d.), fitted in a column oven (CTO-6A, Shimadzu, Japan) to keep the column at ambient temperature. Data was recorded on CR 4A chromatopac (Shimadzu, Japan) run at a chart speed of 10 mm/min.

A degassed mixture of acetonitrile, water and acetic acid (58:38:4) was used as the mobile phase with a flow rate of 1 ml/min. The detections of the peaks were made at 365 nm wavelength with full scale deflection of 0.02 auf. The ratio of peak height of piroxicam to that of internal standard was used as the measure of piroxicam concentration in the sample analyzed.

Pharmacokinetic Analysis

The bioavailability and disposition kinetic parameters of the drug were analyzed on PK II, a computer package for the calculations of pharmacokinetic parameters (8). A compartmental model was selected on the basis of least Akaike Information Criterion (AIC) values (9).

Statistical Analysis

The pharmacokinetic parameters determined in normal and dehydrated rabbits were subjected to a paired t-test to observe the difference between the each set of two conditions. Mean values and their standard errors of mean were computed via a statistical software, SPSS (10).

Results and Discussion (11-24)

Plasma concentration of piroxicam, following oral administration to normal and water deprived rabbits generated biphasic curves in each case (Fig.1). On the basis of AIC values, one compartment open model best fitted the plasma level time data. A highly significant decrease in the plasma concentration of piroxicam was found at all the time intervals in dehydrated condition. The mean±SEM values of all the bioavailability and disposition kinetic parameters are presented in Table 1. The maximum plasma concentrations (C_{max}) of 4.965±0.061 µg/ml and 3.3058±0.092 µg/ml in normal and dehydrated rabbits, respectively, were attained at 1.5 hour post dosing of the drug. The higher osmolarity of blood in dehydrated condition might have interfered with the absorption of the drug as evident from a significant ($P<0.01$) decrease in C_{max} value. A significant reduction in total area under the plasma concentration versus time curve (AUCo-∞) and area under the first moment curve (AUMo-∞) were observed in dehydrated rabbits. The reduction in these parameters may be attirbuted to the highly significant ($P<0.01$) difference in plasma concentration of drug in normal and dehydrated rabbits. A previous study in rats also concluded with similar results for the C_{max}, AUCo-∞ and AUMo-∞ (25). The time to peak plasma concentration (t_{max}) was found similar in all the cases. The half-life

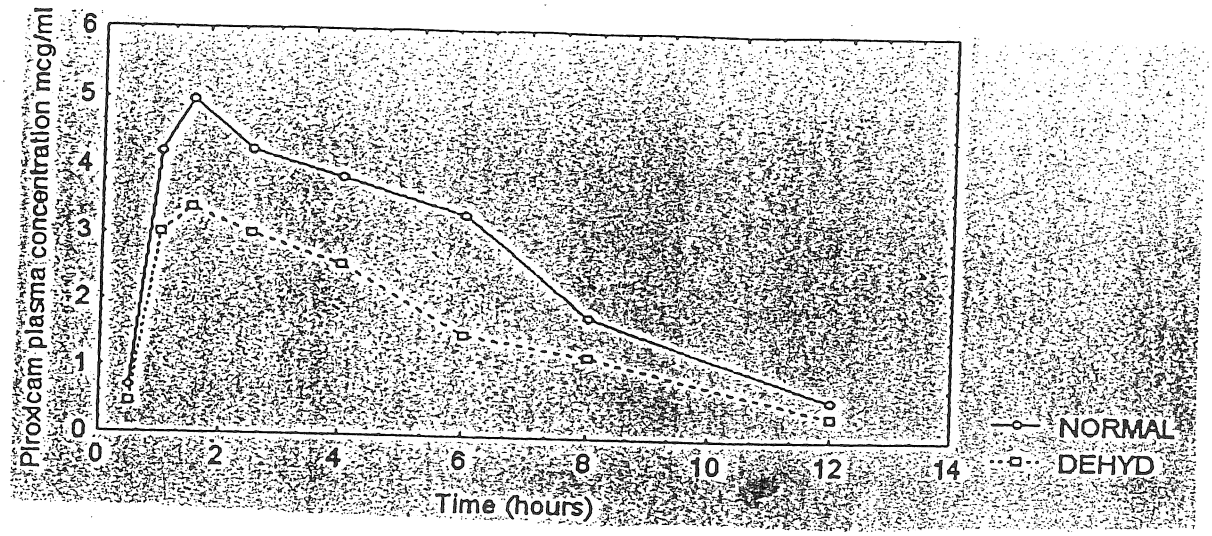

Fig.1.Mean (n=9) plasma concentration of Piroxicam in Normal and Dehydrated rabbits following an oral dose of 5 mg/kg body weight.

Table 1. Mean±SEM (n=9) values of bioavailability and disposition kinetic parameters of piroxicam in normal and dehydrated rabbits following an administration of 50 kg^{-1} single orla dose

Pharmacokinetic Parameters	Groups		Paired
	Normal	Dehyd	t-test
$C_{max}(\mu g.ml^{-1})$	4.965±0.061	3.3058±0.092	**
AUCo-∝($\mu g.hr.ml^{-1}$)	32.056±0.790	21.484±0.809	**
AUMCo-∝ ($\mu g.hr^2.ml^{-1}$)	181.483±6.253	115.744±4.77	**
MRT (hr)	5.652±0.077	5.383±0.037	**
$t_{1/2\ abs}$ (hr)	0.362±0.028	0.3338±0.037	**
$t_{1/2\ elim}$ (hr)	3.403±0.079	3.218±0.044	-
Vd(1)	0.7689±0.017	1.090±0.041	*
Clt ($ml.min^{-1}$)	2.612±0.064	3.9178±0.127	**
t_{max}	1.50±0.00	1.50±0.00	**
Relative bioavailability	100%	67%	-

- = No significant difference
* = Significant difference at 0.05 level
**=Highly significant difference at 0.01 level

values of 3.403±0.079 hr and 3.218±0.044 hr in the normal and dehydrated rabbits, respectively were observed to show a significant ($P<0.05$) difference. The observed $t_{1/2\ elim}$ value is in agreement with the previously reported value of 3-3.5 hr(2). The value of absorption half-life ($t_{1/2\ abs}$) demonstrated a non-significant reduction in dehydrated condition. A significant ($P<0.01$) increase in total body clearance and volume of distribution of the drug was observed in water deprived animals. An increase in volume of distribution and clearance rate of piroxicam might be due to a significant decrease in albumin concentration in dehydrated state (3,4). It was observed that dehydration lowers the relative bioavailability of piroxicam to 67% which points out that dehydration seems to have an effect on the disposition of piroxicam in rabbits. The unbound or free fraction of the drug is

altered by dehydration, and that is available to produce both pharmacologic action and adverse effects. The above findings reveal that additional pharmacokinetic studies of piroxicam is recommended in situations where loss of body water becomes prominent.

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