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Effect of Dehydration on the Pharmacokinetics of Mefenamic Acid

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Abstract: The pharmacokinetic properties and bioavailability of mefenamic acid was studied in normal and dehydrated rabbits. High performance liquid chromatography (HPLC) was used for the assay of mefenamic acid in plasma samples. The mean plasma concentration and area under the plasma concentration-time curve decreased but the volume of distribution and total body

clearance increased significantly ($P < 0.01$) in dehydrated rabbits when compared with normal animals. The results reflect the serious consequences of dehydration on the pharmacokinetics of mefenamic acid.

Key Words: Mefenamic acid, bioavailability, anti-inflammatory drug, pharmacokinetic, dehydration.

Introduction

Excessive loss of biofluids from the body results in dehydration and body water contents become below the normal limits. The most prominent manifestation of water deprivation are loss of body weight and decrease in both blood and plasma volumes (1). Plasma osmotic pressure, plasma protein concentration and hematocrit values increase progressively as water deprivation continues but the pH and acid-base status of the blood remains essentially constant (2-5). A multitude of physiological and biochemical changes has been attributed to transitory dehydration, which can significantly modify the bioavailability and disposition of drugs. These changes in drug disposition kinetics can 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 water deprivation on the pharmacokinetic behavior of mefenamic acid was investigated. Mefenamic acid has analgesic, anti-inflammatory and antipyretic actions and is used for the relief of mild-to-moderate pain in doses up to 500 mg three times daily for the treatment of rheumatoid arthritis. Mefenamic acid is also used to relieve pain arising from soft-tissue injuries, dysmenorrhoea, menorrhagia and other painful musculoskeletal conditions (6-8).

Materials and Methods

Animals

A total of 10 healthy rabbits of both sexes ranging in body weight from 1.2-2.4 kg, were maintained under similar feeding and managemental conditions. The animals were fed fresh green fodder and black gram in the morning and evening, while water was provided ad libitum. A washout period of ten days was given between the two conditions.

Induction of dehydration

Dehydration was produced by keeping the rabbits off water but not food. The body weights of the animals were recorded daily. The animals with a significant increase in total protein level, packed cell volume and 10% decrease in body weight were considered dehydrated.

Drug administration

For the determination of Bioavailability and disposition kinetics of mefenamic acid in normal and dehydrated rabbits, the drug was administered as a single dose of 50 mg/kg body weight (Ponstan suspension, 50 mg/5 ml, Parke Davis & Co. Ltd, Karachi-Pakistan). The preparation was administered through the feeding cannula orally.

Sampling Procedure

Blood (2 ml) was drawn from the jugular vein of the rabbits which were held in wooden cages. The samples were collected in heparinized glass centrifuge tubes with the aid of sterilized disposable plastic syringes just before and at 0.5, 1.0, 1.5, 2.5, 4.0, 6.0, 8.0 and 12.0 hours after the drug administration. The blood samples were centrifuged at 3000 to 4000 rpm for 10 minutes. Plasma was separated and used for the analysis.

Drug analysis

Mefenamic acid concentration in the plasma was determined by the high performance liquid chromatographic procedure described by Hind and Underwood, using ibuprofen as an internal standard (9). The concentration of mefenamic acid in known plasma

samples were determined by comparing the peak height ratio (mefenamic acid/ibuprofen) to that of the standard curve. The plasma levels of the drugs were used to analyze the disposition kinetic parameters of mefenamic acid, applying the one-compartment model of analysis. The PK II computer package was used for this purpose (10).

Statistical analysis

The bioavailability and pharmacokinetic parameters determined in normal and dehydrated rabbits were subjected to a paired t-test to observe the difference between the two conditions. Mean values and the standard error of mean (SEM) were calculated for each parameter using the SPSS program for Windows 6 (11). A value of $P < 0.05$ was taken as being statistically significant.

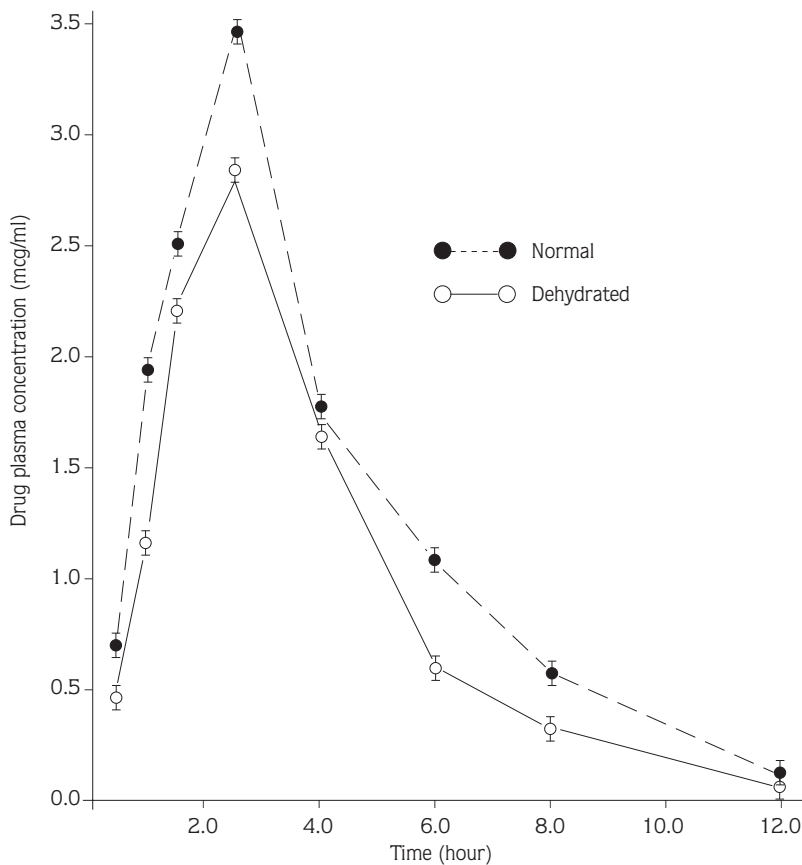


Figure 1. Mefenamic acid plasma concentration-time plot (Mean \pm SEM) after a single oral dose of 50 mg/kg body weight.

Pharmacokinetic Parameters	Animals		Statistical difference
	Normal	Dehydratd	
C_{max} $\mu\text{g/ml}$	3.345 \pm 0.123	2.762 \pm 0.09	**
t_{max} hours	2.5	2.5	ns
AUC_{total} $\mu\text{g}\cdot\text{hr/ml}$	14.954 \pm 0.611	12.004 \pm 0.341	**
$AUMC_{total}$ $\mu\text{g}\cdot\text{hr}^2/\text{ml}$	60.186 \pm 4.715	46.633 \pm 0.341	**
MRT hours	4.157 \pm 0.05	3.883 \pm 0.014	**
$t_{1/2\text{ abs}}$ hours	0.819 \pm 0.053	0.941 \pm 0.052	ns
$t_{1/2\text{ elim}}$ hours	1.865 \pm 0.05	1.607 \pm 0.047	*
K_{abs} hr^{-1}	0.881 \pm 0.068	0.758 \pm 0.052	*
K_{elim} hr^{-1}	0.372 \pm 0.01	0.433 \pm 0.12	**
Vd l/kg	14.694 \pm 0.430	15.653 \pm 0.5	ns
Cl ml/hr/kg	90.972 \pm 1.371	112.85 \pm 1.46	**
Relative bioavailability	100%	80%	

ns = statistically non-significant

* = statistically significant ($P < 0.05$)

** = Statistically highly significant ($P < 0.01$)

Results and Discussions

The mean plasma concentrations obtained after a single oral dose of mefenamic acid (50 mg/kg) in normal and dehydrated rabbits is shown in Figure 1. The maximum plasma concentration of 3.345 \pm 0.123 $\mu\text{g/ml}$ and 2.852 \pm 0.052 $\mu\text{g/ml}$ was attained in normal and dehydrated rabbits, respectively, after 2.5 hours of dosing. From the mean plasma concentration data, a highly significant ($P < 0.01$) decrease was observed in dehydration. Only after the 4th hour a non-significant difference between normal and dehydrated rabbits was observed. The reduction in the drug-plasma concentration in dehydrated rabbits may be attributed to higher osmolarity of the blood, interfering with rapid absorption of the drug from the gastrointestinal tract. Oukessou and Toutain (12) also reported a decrease in ampicillin trihydrate plasma concentration due to water deprivation. The plasma concentration of erythromycin was significantly lower in water-deprived rabbits only during the first hour of drug administration, yielding a significantly lower plasma concentration after an intravenous and oral administration of the drug (13, 14).

The concentration data of mefenamic acid in normal and dehydrated animals generated biphasic curves and according to the Akaike Information Criteria (AIC) values, the one-compartment open model best fits the data in each case. The bioavailability and disposition kinetic parameters of mefenamic acid after an oral administration in both of the conditions are given in Table

Table 1. Bioavailability and disposition kinetic parameters of mefenamic acid in normal and dehydrated rabbits following a single oral dose of 50 mg/kg body weight.

1. A highly significant ($P < 0.01$) decrease in peak plasma concentration, area under the plasma concentration versus time curve and total area under the first moment curve was observed in dehydrated rabbits. No statistical change in half-life, volume of distribution, and absorbance rate constant was noted whereas the values for total body clearance i.e., 90.972 \pm 1.371 ml/h/kg and 112.85 \pm 1.46 ml/h/kg show a significant ($P < 0.01$) increase in dehydrated rabbits when compared with normal animals. These changes may be considered due to higher osmolarity and reduction in blood volume in dehydrated rabbits (15). A reduction in blood volume as a result of shock of varying etiology, has profound effect on haemodynamics and a drastic alteration in hepatic clearance can occur. Again, problem arises in attributing the latter to perfusion changes, which alter drug delivery and extraction, or to reduce oxygen supply to the liver and the mixed-function oxidase system (16).

In the present study, the mean time to reach peak plasma concentration (t_{max}) was found to be 2.5 hours which is in accordance with the previously conducted studies on mefenamic acid in rabbits (17, 18). Oukessou and Toutain (12) reported a low systemic availability of ampicillin and changes in its disposition during water deprivation which was linked to adaptation of renal function as assessed by inulin and PAH (para-amino hippuric acid) clearance. The same factors also contribute the difference in the bioavailability and disposition kinetic parameters of mefenamic acid in normal and dehydrated

rabbits. Keeping AUC_{total} of the normal rabbits as 100%, the relative bioavailability of mefenamic acid in water deprived rabbits is 80% which is in accordance with the results of Hamaguchi et al (18).

The clinical inference of the above data can be associated to the dosing of mefenamic acid when utilizing

this drug on long-term basis. The steady-state of mefenamic acid in water deprived animals will be distinct when given the equivalent dose. Consequently, an outstanding concern in monitoring patients on continued remedial treatment is essential.

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