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INFLUENCE OF THE RAW MATERIALS OF DIFFERENT ORIGINS ON THE BIOAVAILABILITY AND PHARMACOKINETIC PROPERTIES OF IBUPROFEN IN HUMAN VOLUNTEERS

ATIF RAZA[1], NADEEM IRFAN[2], MAHMOOD AHMAD[2], SHADAB QAMAR[3]

[1]Faculty of Pharmacy, University of the Punjab, Lahore, Pakistan
[2]Department of Pharmacy, Islamia University, Bahawalpur, Pakistan
[3]Pakistan Council for Scientific and Industrial Research (PCSIR) laboratory, Lahore, Pakistan

In a random cross over study, 6 healthy human volunteers received single dose of 400 mg of ibuprofen raw materials I and II orally at two distinct sessions after an overnight fast. The bioavailability of the two raw materials differ significantly as judged by AUC and peak plasma concentrations were found to be bioequivalent since both of the materials demonstrated absorption within 20% confidence limit.

Keywords : *Ibuprofen; Bioavailability; Pharmacokinetic*

Introduction

The bioavailability of drug is greatly influenced by its physical state, dosage form and the way by which it is manufactured(1). A given drug may show different availability from the same dosage form, made by different manufacturers. There is also a possibility of different availability from lot to lot of a drug produced by the same manufacturer(2).

The present project was planned to investigate the influence of the source variations of raw materials on the bioavailability and disposition kinetics. This study provides data on the bioavailability of drugs and is helpful to select a proper manufacturer of active raw materials for a specific drug. For this purpose ibuprofen was selected as a drug of choice because it has been used extensively for its analgesic (3,4), antipyretic, antirheumatic and anti-inflammatory actions (5, 6).

Materials and Methods

Subjects

Six male human volunteers having 21-26 years of age and with mean body weight of 65 kg were selected for the study. The subjects were designated as A, B, C, D, E and F. These volunteers were deemed healthy on the basis of their complete physical examination and clinical investigations. Personel history was noted to check the drug allergy and other major illness in the past. There was no history of ingestion of any drug two weeks prior to the study. The written consent about the objectives and method of the study was obtained from each volunteer.

Candidate raw materials

The two sources of ibuprofen were labeled as source I and source II. Source I was of Chinese and source II was of Korean manufacturers' products.

Study Design

In a cross over and comparative study design, six subjects received 400 mg as a single dose of either source of ibuprofen on two distinct sessions with a washout period of two weeks.

Drug Administration

The measured amount of ibuprofen raw materials I and II was filled in the empty capsules separately and were used for administration to the overnight fasted volunteers. Two hours after ingestion of the drug, a standard breakfast was served to all the participants whereas lunch was given after six hours of post dosing on each study day.

Blood Sampling

A sample of 5 ml of whole blood was taken with 5 cc disposable syringe from the fore-arm vein immediately before dosing and at 0.5, 1.0, 1.5, 2.0, 4.0 6.0 and 8.0 hours after administration of the drug. The blood samples were centrifuged at 3000 rpm for 10 minutes and the separated plasma samples were frozen until just prior to assay.

Drug analysis

High performance liquid chromatographic method was used to quantify the drug in plasma samples (7).

Bioavailability an disposition kinetic parameters

All the pharmacokinetic parameters were calculated on a computer package "PKII"(8). The absorption parameters including, peak plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration time curve (AUC), first moment of plasma concentration time curve (AUMC), mean residence time (MRT) and absorption half-life ($t_{1/2^{abs}}$) were assessed. The drug disposition parameters like elimination half-life ($t_{1/2^{elim}}$), apparent volume of distribution (Vd) and total body clearance (Clt) were calculated.

Statistical Analysis

The bioavailability and pharmacokinetic parameters were obtained from the individual plasma concentrations Vs time curves. The bioavailability and pharmacokinetic parameters were compared between two treatments of each raw material by a paired t-test. A window based computer software, SPSS was used for this purpose(9).

Results and Discussion

Ibuprofen was used for the study of source variation, due to basic manufacturing on the bioavailability and pharmacokinetics of drugs. Plasma concentrations (mean±SEM) of ibuprofen I and ibuprofen II in six human volunteers, following an oral single dose of 400 mg, were determined (Table 1, Fig. 1)

Table 1. Plasma concentration-time data (Mean ± SEM) of Ibuprofen I and II after an oral dose of 400 mg in Human Volunteers (n=6)

Time in Hours	Ibuprofen I	Ibuprofen II
0.5	10.27±0.16	10.08±0.03
1.0	15.58±0.38	15.70±0.28
1.5	20.02±0.50	20.82±0.27
2.5	14.34±0.31	14.10±0.18
4.0	7.79±0.06	8.03±0.02
6.0	4.08±0.04	4.10±0.07
8.0	1.99±0.03	1.92±0.03

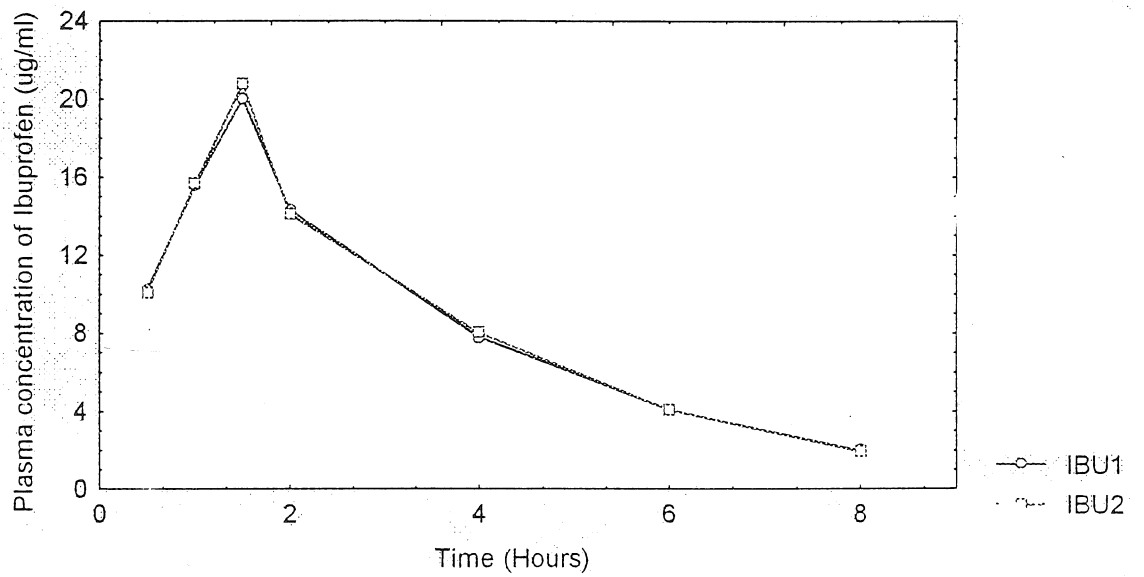

Fig.1. Mean plasma concentration of Ibuprofen 1 and 2 in six healthy volunteers following oral dose of 400 mg each.

It is evident from the figure that there is no difference in concentrations at all the sampling times between ibuprofen I and II. This data was used to calculate the bioavailability and pharmacokinetic parameters. These parameters were compared for ibuprofen I and II (Table 2). The peak plasma levels of 20.02±0.50 µg/ml 20.82±0.27 µg/ml were reached in 1.5 hours for ibuprofen I and II, respectively after the administration of the raw materials. There is no statistical difference between these two levels. Mean±SEM value of the total area under the plasma concentration-time curve for ibuprofen I and II are 71.41±0.407 µg.hr/ml and 71.23±0.448 µg.hr/ml respectively. Based on these results, the bioavailability of both materials is very good and almost identical and at the same time statistically insignificant. The mean±SEM area under the first moment curve (AUMC) was found to be 249.13±0.650 µg.hr^2/ml and 246.24±1.46 µg.hr^2/ml for ibuprofen I and

Table 2. Bioavailability and Pharmacokinetic Parameters of Ibuprofen I and Ibuprofen II after an oral dose of 400 mg in Human Volunteers (n=6)

Pharmacokinetic Parameters	Raw Materials		Statistical differences
	I	II	
C max (cal) hr	17.4342±0.283	17.5115±0.188	-
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t 1/2 abs (hr)	0.36666±0.015	0.3634±0.013	-
t 1/2 elim (hr -1)	1.9429±0.012	1.9166± 0.009	+
AUC 0-∞ (mg.hr/ml)	71.4120±0.407	71.2367±0.448	-
AUC 0-∞ (mg.hr^2/ml)	249.1367±0.650	246.24±1.66	+
MRT (hr)	3.4917±0.022	3.4594±0.002	+
Clt (ml/min)	116.70±0.658	117.00±0.742	-
Vd (litres)	19.63±0.215	19.41±0.182	-
Relative Bioavailability	100%	99.75%	

- = Nonsignificant difference
+ = Significant difference

II, respectively. AUMC is the total area under the curve resulting from a plot of the product of drug concentration and time versus time, which was calculated by means of trapezoidal rule. The values of AUMC differ significantly when both of the raw materials are compared.

The ratio of AUMC to AUC for any drug is a measure of its mean residence time, MRT(10). The mean±SEM values for MRT of ibuprofen I and II were found to be 3.4917±0.022 hr and 3.459±0.002 hr, respectively which differs statistically. Actually, MRT is analogy to drug half life. It provides a quantitative estimate of the persistence time of a drug in the body. Like half-life, it is a function of both distribution and elimination and indicates the time required to eliminate 63.2% of the dose (10). Absorption half-life of ibuprofen I and II did not show any difference statistically while the elimination half life, i.e., 1.9429±0.012 hours and 1.9166±0.009 hours for ibuprofen I and II, respectively are statistically different. The total body clearance of ibuprofen I and II were 116.70±0.658 and 117.00±0.742 ml/min, respectively. These values are not different statistically. Likewise, values for volume of distribution were also the same for ibuprofen I and II, which were 19.63±0.215 and 19.41±0.182 liters, respectively. Keeping source I as standard, the relative bioavailability of source II was observed to be 99.75%. The results showed that, as the limits given by Westlake(11), both of the sources of ibuprofen were bioequivalent.

References

1. Gibaldi, M.: Biopharmaceutics and Clinical Pharmacokinetics, pp. 1-26, Lea Febiger, Philadelphia, 1985
2. Searl, R.O., Pernarowski, M.: Can. Med. Assoc. J. 96, 1513 (1967)
3. Pulkkinen, M.O., Csapo, A.I.: Prostagladins 15 (96), 1055 (1978)
4. Owen, H.: Br. J. Anaesth. 58, 1371 (1986)
5. Adams, S., Mc Callough, K.F., Nicholson, J.S.: Arch.Lnt.Pharmacodyn. Ther. 78(1), 115(1969)
6. Switala, M., Garulinski, T., Obminska-Domoradz Ka, B., Debowy, J.: J. Pharmacol. Pharm. 40(3), 265 (1988)
7. Poirier, J.M., Lebot, M., Cheymol, G.: Ther. Drug. Moint. 14(4) 1322 (1992)
8. Johnston, A. and Woollard. PKII (computer program) MS-DOS version 2.02, © UK (1988)
9. SPSS (Window-based computer program) Version 6, © SPSS Inc. USA (1993)
10. Yamaoka, K., Nakagaw, T., Uno, T.: J. Pharmacokin. Biopharm. 6, 547 (1978)
11. Westlake, W. J.: Biometrics 32, 741 (1976)

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