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PHARMACOKINETICS DIFFERENCES OF TAB MEFENAMIC ACID (MA) 5OOmg (ONE PILL) AND 250mg (TWO PILL) WITH AND WITHOUT FOOD

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ABSTRACT: Administration of two tab instead of one double strength tab is more often ordered by the physicians, pharmacists and even selected by the patients in case of over the counter drugs. In order to determine the ultimate quality of any formulated dosage form and rationalize the therapeutic plan as well as to individualize the prescription, in vivo measurement of drug is the modern and specialized expertise of the clinical *I* research area of pharmacy practice, which provides effectiveness and assures the safety of drugs. All pharmacological, therapeutic or toxic responses are subject to reaching of drug at the site of action through connective tissue. Other than physico-chemical properties of drug, there are numerous factors from manufacturing process to biochemical behaviour of the individual, which resist in the absorption, distribution, metabolism and elimination of drugs in the biological system.

Tab MA Test II (250 mg) & Test I (500 mg) conventional formulations manufactured by local industries were investigated for bioavailability followed by pharmacokinetic studies on adult, male, healthy, human local population. A sensitive, specific and validated method was developed for the estimation of MA in blood. HPLC was performed on a reversed phase CIs column (flow rate 1.0 ml/min, UV= 280 nm) with 10 mM buffer of KHzP04 (adjusted pH 2.9 with Phosphoric Acid) and Acetonitrile (70:30) where as extraction of the drug from the plasma was carried out by deproteinization of plasma according to classical method described by Roohi Obaid *et ai*. 2002. Oral administration of MA Tablet Test I (single tab of 500 mg) and Test II (two pills of 250mg) with and without food to 12 healthy human volunteers was conducted. Peak level (T max) of MA tablet 500 mg (single tab) and 250 mg (two pilIs) of was observed at about 105 and .240 minutes without and with food respectively. Two pills of MA; Test II showed significantly increase the AUC and Cmax value in both cases either drug is administered with food or without food.

Keywords: Mefenamic acid, Bioavailability, OTC, Non-steroidal anti-inflammatory.

INTRODUCTION

Mefenamic acid (MA) is an oral non-steroidal anti-inflammatory agent. Mai s used as an analgesic and to provide relief in primary dysmenorrhea. It has antipyretic activity. The FDA approved MA in 1967. It is used in symptomatic treatment of moderate to severe inflammatory and degenerative arthritis, primary dysmenorrhea, tension headache, postoperative and post-traumatic pain; short-term treatment for chronic pain, cancer pain (especially with bone metastasis).

Bioavailability:

The extent of absorption is measured by the bioavailability, or fraction of dose absorbed measured by the area under the concentration-time profile (AVC), whereas the rate of absorption is roughly assessed by measuring the maximum plasma or blood level, Cmax, of a compound (Mangione, 1998) Although C.nax is a function of both the rate and extent of absorption, and some have argued that T_{max} would be a more pure measure of the rate of absorption, Cmax is a clinically relevant parameter in most cases. Many excipients can affect the absorption of drugs. In addition, any sensitivity the patient may have to the various colorants and preservatives present must be taken into account.

Patient Variation and Other Determinants of Bioavailability:

Differences in bioavailability also arise from one patient to another. In some cases, the difference is due to gender. For e.g. women have half the GADH activity of men. Thus, it is not the smaller stature of women that causes increased intoxication from ingested alcohol, but rather the greater bioavailability of the alcohol. (Barr, 1991) In other cases, differences can be attributed to ethnicity or race. For example, one study showed that calcium, which is actively absorbed in the small intestine, has a higher bioavailability in young black girls (44%) than in young white girls (25%) (Johnson, 1997). Indeed, the state of health is a determinant of the activity of CYP3A4. The metabolism of drugs by CYP3A4 may be suppressed by interferon, which is released during infection. Thus,

a patient previously stabilized on a maintenance medication (e.g. cyclosporine) who receives an antibiotic for an upper respiratory tract infection may experience an increase in plasma concentrations. This may be falsely attributed to a drug-drug interaction when in fact it is a biochemical change due to infection (Gillum, 1993).

Effect of Food on Bioavailability:

Historically, the presence of food in the gastrointestinal tract was regarded as a barrier to absorption. This led to the suggestion that drugs should be taken on an empty stomach when possible. However, it is now recognized that interactions between food and drugs must be examined on an individual basis (Chairman, 1997). Changes in absorption and bioavailability may be due to secretion of gastric acid, bile, and pancreatic fluids; modifications of gastric and intestinal motility patterns; and alterations in blood flow. In a patient with decreased acid secretion leading to a higher than normal gastric pH, weakly basic drugs can have lower bioavailability due to poor dissolution rates. For example, ketoconazole, a weak dibasic drug, exhibits pH-dependent dissolution. When ketoconazole was administered with ranitidine, an H2 blocker that causes an increase in gastric pH, the bioavailability of ketoconazole decreased 95%, with its peak plasma level dropping from 8.2 to 0.6 mcg/mL. Similar results on ketoconazole bioavailability were seen when the gastric pH was increased by cimetidine (Chairman,
1997), Enoxacin, a quinolone antibiotic, is very soluble at pH values less than 4.5, but the solubility drops dramatically above pH 5. Co-administration of enoxacin with ranitidine (to increase gastric pH) decreased peak plasma levels by 45% and bioavailability by 32%. In addition, when famotidine is co-administered with dipyridamole, another weak base, it reduces the peak concentration by 79% and the bioavailability by 37%(Chairman, 1997).

These data show that for many weakly basic drugs, the peak concentration is substantially reduced due to a lower rate of dissolution. However, the reduction in bioavailability, while significant, is not as great as the reduction in peak concentration. The bioavailability *of* weakly basic drugs can be compromised particularly lipophilic drugs may offset the potentially limiting effects of gastric pH by way of bile-mediated dissolution and increased residence time in the upper GI tract.

Effect of Fatty M~als:

Ingestion of lipids decreases gastric motility, leading to an increase in gastric residence time. The presence of lipid digestion products within the upper small intestine induces secretion of biliary and pancreatic fluids. Bile salts have a number of actions in the gut that can affect bioavailability. For example, bile salts are surface-active agents that can solubilize poorly soluble drugs. They can also increase the dissolution rate by improving wetting of the surfaces of relatively hydrophobic drug particles in the intestine. In addition, bile salts may alter the intrinsic permeability of the intestinal membrane, leading to increase intestinal absorption. All of these effects can improve the bioavailability of poorly water-soluble drugs. (Charman, 1997). Griseofulvin is a classic poorly soluble and poorly wettable drug. Its bioavailability increases dramatically after a meal. This increase was shown to be the result of enhanced solubility and dissolution in the presence of bile salts. Atovaquone, a highly lipophilic antiprotozoal drug, is slowly and irregularly absorbed upon oral administration in the fasted state. Administration with a low-fat or high-fat breakfast improved bioavailability 330% and 530%, respectively (Charman, 1997). There are a number of poorly water-soluble drugs, however, whose absorption is not enhanced by the presence of bile salts. In fact, they form insoluble drug-bile salt complexes that lead to a decrease in bioavailability. These include neomycin, kanamycin, and various large molecular weight antibiotics (Charman, 1997).

Bioequivalence:

Two or more chemically or generic equivalent products of the same preparation can be said to be bioequivalent, if they do not differ «20%) significantly in their bioavailability characteristics. This bioequivalent drug is assumed that they will be therapeutically equivalent and can be use interchangeably (F.D.A. (1997) Draft Guidance for industry).

MATERIALS AND METHODS

In vivo trial was conducted according to international guidelines for in vivo studies. The bioavailability of MA 500 mg Test I (Single. pill) and MA 250 mg Test n (Two pills) tablets was evaluated by plotting blood free concentration profile df drug at different intervals after oral administration with and without food followed by pharmacokinetic calculations.

Subjects:
A subject panel of 6 healthy adults, male, human volunteers of an average age of 25.4 years [J 5. 4 ranging from 19 years to 38 years, mean height of 5.1 [j 0.0 ranging from 5.03 to 5.10 and an average weight of 59.3 kg 12.4 ranging from 47 kg to 87 kg participated in the study.

Selection of volunteers:
Selection criteria for volunteer inclusion in this study was:
No history of allergic tendencies and reaction to fumarate derivatives or any other ingredient used in the formulation of Test drugs With normal blood counts, normal liver and kidney function tests, and without abnormalities in physiology, urine and blood analysis.

V olunteers should be free of any treatment or any drug for at least a month prior to study.

Absence of any chronic or pathological disease.

The panel members were given a general medical examination to establish good health. The following selection criteria were used for this purpose.

No congenital disease. No
underline hypertension.

Response of the following were checked and found normal.

Hepatic
Gastrointestinal tract
Respiratory tract
Neurological
Renal
Psychiatric Metabolic
Cardiovascular

Exclusion Criteria:
Subjects with any current or past medical condition that might significantly affect their pharmacokinetic and pharmacodynamics response to the administered drug were the limiting factors in the study.

All volunteers were thoroughly informed about the aims and objectives of the study, the drug to be tested, and the hazards/ side effects of the drug MA and also their rights to separate themselves from the study at any stage without mentioning any reason. Informed consent and their willingness were also obtained from each subject selected to participate in the study.

Restrictions:
No volunteer was allowed to take any prescription or OTC drug one week prior to dosing and during the study period, in order to avoid interference with the kinetic behavior of MA in the body or in the determination of drug in the blood. The volunteers were instructed to report the investigator about the illness/side effects and the treatment undertaken. No volunteer took any drug for at least one month prior to and during the study.

Table 1 Demographic Characteristics of healthy volunteers participated in the study

Studv d .

Sub ID	Name	Age Years	Weight kg	Height ft
A	M. Imran Asim Khan	23.00	59.80	5.09
B	Imran DI Haq	24.00	55.30	5.09
C	Javed Sattar	28.00	87.00	5.10
D	Mohammad Rehan	19.00	52.00	5.03
E	Mohammad Irfan Khan	26.00	52.00	5.06
F	Zubair M. Khan	22.00	47.00	5.04
J	Habib Dr Rehman	20.00	53.00	5.03
K	Tariq Mahmood	22.00	56.00	5.06
L	Mohammad Naeem	38.00	76.00	5.08
M	Zahid Hussain	32.00	72.00	5.06
N	Mohammad Ayaz	27.00	52.00	5.03
0	Sohail Nasir	24.00	49.00	5.05
Mean + SD		25.4	59.3	5.1
-		5.4	12.4	0.0

Study conducted on four occasions. Volunteers were divided into two equal groups A and B and subdivided into AI, A2, BI & B2 accordingly. On first occasion and second occasion, group Aland A2 were administered two tablets of Test II without food and with food respectively under close observation. On third and fourth occasions group Bland B2 were administered one tablet of Test I without and with food respectively. Samples were collected and analyzed accordingly.

Single Dose-Single Period Study:
In this study, each subject is successively exposed to a single treatment on a single occasion. Blood samples

Table 4 Effect of food on the Clllax (ng/ml) & Tlllax (minutes) of Test II oral administration in human volunteers

Parameters	Test II	
	Without food	With food
Clllax (ng/ml)	2049	3169
Tlllax (minutes)	105	240

Table 4 Effect of food on the absorption and AVC (ng. mllhours) of Test II and Test I oral administration in human volunteers

MA	With food	Without food	Increased	Factor
Test II	23156	12299	47%	1.9
Test I	11365	8672	24%	1.3

Table 5 Difference in blood profile of MA when taken single pill of Test lor 2 tab of Test II

Minutes	Test II	Test I	Diff. Factor
0	0	0	0
30	583	210	2.78
60	1267	1236	1.03
75	1737	1937	0.90
105	2016	2345	0.86
120	1869	2177	0.86
240	2438	2169	1.12
420	1037	1019	1.02

Table 6 Difference in blood profile of MA when taken single pill of Test I or 2 tab of Test II without food, n = 6

Minutes	Test II	Test I	Diff. Factor
0	0	0	0
30	528	200	2.64
60	892	1421	0.63
75	1382	2195	0.63
105	2049	3133	0.65
120	1929	2730	0.71
240	1707	1307	1.31
420	852	525	1.62

Table 7 Difference in blood profiJe of MA when taken single pill of Test I or 2 tab of Test II with food, n = 6

Minutes	Test II	Test I	Diff. Factor
0	0	0	0
30	638	220	2.90
60	1643	1051	1.56
75	2091	1680	1.24
105	1984	1556	1.28
120	1810	1625	1.11
240	3169	3031	1.05
420	1221	1512	0.81

Phamiacokinetic and Statistical Analysis

Chromatograms of all samples were readl calculated in the context of standard calibration curve after system suitability test. The plasma drug concentration levels were monitored and analyzed statistically in order to evaluate bioavailability, pharmacokinetic and other parameters of the studied formulation. MS Excel 98 program was used for the calculation of peak concentration (Clllax), time to peak concentration (Tlllax) while area under the curve (AVC) was calculated by trapezoidal method. Other pharmacokinetic values were calculated by manual technique using basic mathematical tools.

DISCUSSION AND CONCLUSION

Three basic following pharmacokinetic parameter were calculated for the tested products i.e. Tablet Test I mg (a conventional release oral formulation).

Area under curve (AVC)

Peak Concentration Clllax

Time to peak concentration T Illax

AVC

With Food: Two tab of Test II showed double value as compared to the single tab of Test I

Without Food: Two tab of Test II showed higher value as compared to the single tab of Test I and food intake increases the residence time in both cases.

Data revealed that 2 single pill of Test II has more residence time than the single pill of Test I.

Peak Concentration Clllax

With Food: Two tab of Test II did not alter the c'nax of single dose of Test I mg

Without Food: Two tab of Test II did not alter the Cnax of single dose of Test I while two tab of Test II with food intake increases the Cmax.

Time to peak concentration T

max

Food intake significantly increases the time of drug to reach their maximum concentration in both cases. And no significance difference was observed in T max after the single dose of Test I in single pill or two pill of Test II locally manufactured MA in Pakistani volunteers.

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