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PHARMACOKINETICS OF TWO 200 MG IBUPROFEN FILM-COATED TABLETS AND AN EFFERVESCENT TABLET

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ABSTRACT

The pharmacokinetics of two 200 mg ibuprofen (IP) film-coated tablets and a 200 mg effervescent tablet were studied in cross-over fashion on 14 healthy volunteers. After ingestion of the novel film-coated tablet, absorption half life (0.6 h) was 42-50 % ($p<0.05$) shorter, C_{max} (24.6 mg/l) was 38-42 % ($p<0.05$) higher and t_{max} (1.4 h) was 33-36 % ($p<0.05$) shorter than after the older type film-coated tablet and after effervescent tablet, respectively. The bioavailability of IP was close to similar from the three preparations. IP was tolerated without side-effects. The faster absorption of IP from the new film-coated tablet may have therapeutic significance when rapid onset of effect is desirable, e.g. in the treatment of fever and migraine.

INTRODUCTION

Ibuprofen (IP) is a propionic acid derivative, a non-steroidal antiinflammatory drug (NSAID). IP has many clinical indications, such as fever, rheumatic and other pains, rheumatic inflammation, migraine and dysmenorrhea (1,2,3). Until recently, in most countries only acetylsalicylic acid was available as an over-the-counter NSAID, but now IP is permitted to

be sold at 200 strength in e.g. Nordic countries without prescription. Over-the-counter IP with its many indications represents a challenging commercial possibility. Therefore several new brands of IP products have been introduced, and new pharmaceutical formulations and dosage forms have been developed. In this study we investigated the pharmacokinetics of two film-coated 200 mg IP tablets, one new and one already on the market, as well as those of a new 200 mg effervescent tablet.

MATERIALS AND METHODS

Fourteen healthy, non-smoking volunteers (Table 1) were subjected to a clinical examination and laboratory tests before the trial. There were no pathological values in the results of the blood laboratory tests. Regular medication during the four weeks prior to the start of the trial or occasional medication or ingestion of alcohol during the 24 h before the study were exclusion criteria, as were pregnancy and lactation. The use of contraceptive drugs was allowed.

The study was carried out in three sampling runs with one week intervals, in cross-over fashion. The drugs were given to the volunteers in a randomized order (Table 1). Subjects fasted from 2200 o'clock of the day before the start of each sampling run of the study. At 0800 of the study day, the film-coated tablets were administered with 2 dl of tap water; effervescents were given dissolved in 2 dl of tap water. At 1200 o'clock they were given a low fat, standardized meal, and at 1500 o'clock, a standardized snack. Venous blood samples (5 ml) were drawn into vacuum tubes using 20 G needles before the ingestion and 20, 40 60, 80, 100 min, 3, 4, 6, 8, 12 and 24 h after the administration. Serum was separated from the blood samples by centrifugation and stored at -20^{0}C until analysis.

Volunteers filled out a study event form after each sampling run stating the type, time, intensity and duration of each adverse event. A signed consent was given by all the volunteers before the trial. The design of the trial was approved by the Ethics Committee of the University of Kuopio and Kuopio University Central Hospital, Kuopio, Finland.

Analytics and calculations

Serum IP concentrations were measured with a HPLC method (4). The quantitation limit was 0.1 mg/l (signal to noise ratio 4:1).

Arithmetic means and standard deviations (S.D.) from serum IP concentrations were calculated. Pharmacokinetic parameters were calculated using PCNONLIN pharmacokinetic computer program (version 02; Statistical Consultants, Kentucky, USA). One compartment model with

TABLE 1

The Anthropometric Data of the Volunteers, and the Administration Order of 200 mg Ibuprofen Film-Coated Tablets Burana® (B200) and Dolgit® (D200), and Effervescent Tablet (E200).

Volunteer	Sex (F/M)	Age (y)	Weight (kg)	Height (cm)	Administration order sampling runs I	II	III
A	M	22	83	195	D200	B200	E200
B	M	22	65	169	D200	E200	B200
C	M	22	71	177	B200	E200	D200
D	F	22	49	155	D200	B200	E200
E	F	24	50	156	E200	D200	B200
F	M	23	65	168	B200	D200	E200
G	F	25	78	174	B200	E200	D200
H	M	23	83	187	E200	D200	B200
I	F	21	70	161	E200	D200	B200
J	M	25	75	188	D200	E200	B200
K	F	23	58	165	E200	B200	D200
L	F	23	55	169	D200	B200	E200
M	M	25	80	178	B200	D200	E200
N	F	24	55	160	E200	B200	D200

first-order input and first-order output with the possibility of lag-time of absorption was used for iterative minimization of the function. The parameters were t_{lag} (lag-time of absorption), AUC (area under the concentration/time curve from zero to infinity), C_{max} (maximum concentration of IP in serum), t_{max} (the time of the occurrence of Cmax), $t_{½,01}$ (half life of absorption) and $t_{½,10}$ (half life of elimination).

Two-way analysis of variance was used to determine the statistical significance of the differences between products in the pharmacokinetic parameters. Statistical tests and comparisons were evaluated at the 95% significance level ($p<0.05$). All statistical calculations were performed using SPSS/PC+ program (version 2.0, SPSS Inc., Illinois, USA).

The statistical power of the study to detect differences between preparations in the pharmacokinetic parameters was calculated using the MathCad computer program (version 2.5; MathSoft Inc., Massachusetts, USA) with the following parameters: the maximum allowed type I (alpha) error 0.05, and the maximum allowed type II (beta) error 0.2.

Preparations

B200: Burana® film-coated tablet, 200 mg. Oy Medipolar, Oulu, Finland. Batch OK148A.

D200: Dolgit® film-coated tablet, 200 mg. Dolorgiet Arzeinmittel, St. Augustin, Bonn, Federal Republic of Germany. Batch 290299.

E200: Ibuprofen effervescent tablet, 200 mg. Dr Gergely, Vienna, Austria. Code 211189/1.

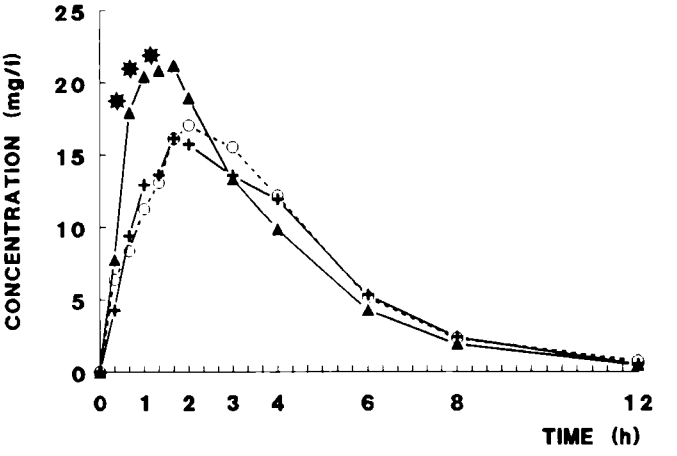

FIGURE 1

Serum Concentrations (means from 14 volunteers) of Ibuprofen After a Single 200 mg Dose as Film-Coated B200 Tablet (-+-), Film-Coated D200 Tablet (-▲-), or as an Effervescent E200 (--o--). * = Significantly ($p<0.05$) Higher than B200 and E200, ANOVA + Tukey's Test.

The mean IP contents (measured using the method described in the assay of IP for IP tablets, United States Pharmacopeia XXII, 1990) of the preparations were: B200 194.8±1.0 mg, D200 194.0±0.5 mg, E200 201.4±0.6 mg (means±S.D., N=6).

RESULTS

The volunteers reported of no adverse events after taking IP. The concentrations of IP in serum are shown in Figure 1. In the last (24 h) blood samples IP levels were below the quantitation limit.

The bioavailability of IP was close to similar from all three products, but IP was absorbed faster from D200 than from B200 or E200. After ingestion of D200, C_{max} (24.6 mg/l) was achieved 0.7 - 0.8 h earlier ($p<0.05$), and it was 6.8 - 7.3 mg/l ($p<0.05$) higher. This can not be explained by statistically insignificant differences in lag-times (Table 2).

DISCUSSION

Peroral bioavailability of IP is close to 100 % (5), and in general it is not altered by pharmaceutical differences in IP products. Our results confirm the previous findings

TABLE 2

Pharmacokinetic Parameters of Ibuprofen (means ± S.D. from 14 volunteers) Calculated from Concentrations in Serum After a Single Peroral 200 mg Dose.

	t_{lag} (h)	$t_{½,01}$ (h)	t_{max} (h)	C_{max} (mg/l)	$t_{½,10}$ (h)	AUC (mg/lxh)
B200, film-coated tablet						
mean	0.40	1.04	2.04	17.8	1.42	81.0
±S.D.	0.37	0.55	0.77	4.5	0.27	17.8
Comparison between B200 and D200						
Power	NM	29.9*	26.9*	25.8*	12.7	11.1
D200, film-coated tablet						
mean	0.27	0.60	1.36	24.6	1.29	81.3
±S.D.	0.19	0.43	0.55	8.3	0.36	19.9
Comparison between D200 and E200						
Power	94.4	88.6*	30.9*	21.1*	10.9	15.4
E200, effervescent tablet						
mean	0.27	1.19	2.11	17.3	1.46	84.3
±S.D.	0.29	0.56	0.64	5.4	0.30	27.4
Comparison between E200 and B200						
Power	92.9	33.7	16.2	15.1	11.3	13.2

Power = minimum difference (%) that could be detected. NM = >100; not accurately measurable
* = statistically significant ($p<0.05$) difference; ANOVA + Tukey's test.

about the stable bioavailability of IP from different formulations. Our study on 14 volunteers was extensive enough to detect differences larger than ±15.5 % in AUC values and larger than ±12.7 % in elimination half lives. No significant differences were observed.

Food can delay the dissolution and absorption of IP (6). Liquid formulations are usually least affected by the contents of the stomach. In the present study, volunteers fasted for 10 h before drug administration, and they were given a low fat meal four hours after the administration of preparations. Therefore the food obviously did not affect the absorption of IP either from solid form tablets or from effervescent tablets.

In general, liquid formulations of drugs produce the most rapid and the most complete absorption of peroral drugs. The results obtained after ingestion of dissolved effervescents did not show the expected superiority. Already previously, some studies have shown that the absorption of IP from liquid formulations is slower than from solid form tablets. Friedman et al. (7) observed that IP was absorbed more slowly from suspension than from tablets. Absorption of IP from solution have been shown to be more rapid than from suspension (8). Small et al., (9) found slower absorption of IP from tablets disperged in cherry syrup or in Coca-Cola than from solid form tablets or from IP dissolved in orange juice. This finding suggests that IP may be incompletely dissolved in some liquids; in the case of effervescent tablets, in water. Incomplete dissolution results in an IP liquid that resembles suspension in its pharmacokinetic properties. In vitro, the pH of the dissolution medium have been found to affect markedly the dissolution of IP (10).

The age of the patient, liver disease or rheumatoid arthritis have minimal effects on absorption or bioavailablity (11), but in several earlier studies, the absorption rate of IP has been shown to be affected by pharmaceutical differences in products (4,12,13) and by the route of administration (8). With respect to the rate of absorption, we could reliably show large differences between preparations: 50 - 55 % in tmax and 74 - 99 % in absorption half lives. There were also differences in peak plasma IP concentrations, the rapidly absorbed film-coated tablet producing the highest levels. Differences of this magnitude may have significance in therapy, especially as over-the-counter 200 mg IP preparations are most commonly used against acute symptoms, where a rapid drug action is desirable.

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