International Journal of Pharmaceutics, 44 (1988) 9–14
Elsevier

IJP 01475

Research Papers

Effect of milk and food on the bioavailability of ketoprofen in man

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(Received 22 October 1987)
(Accepted 17 November 1987)

Key words: Ketoprofen; Milk; Food; Excretion; Bioavailability

Summary

The influence of milk and of a standard breakfast on ketoprofen bioavailability from commercial capsules was studied in 4 healthy volunteers. The drug was administered as a single oral dose of 50 mg. Evaluation of the absorption rate was done by means of urinary excretion measurements. Eight urine samples were collected over a 24-h period following ketoprofen administration and the drug urine concentrations were determined by HPLC. The data were statistically analyzed by the *t*-test for paired observations. Milk significantly reduced the extent of ketoprofen absorption, while both the rate and extent of absorption were significantly reduced by food.

Introduction

Many patients take medication at meal time to decrease side effects on the gastrointestinal tract. Milk is also a demulcent fluid with which the administration of drugs is very convenient. However, there is considerable evidence that the rate and extent of drug absorption may be influenced by the presence of solid or liquid exogenous substances in the gastrointestinal tract (Hamaguchi et al., 1986). Dietary effects on drug absorption are variable and frequently depend on the type of diet as well as on the physicochemical properties of the drug and the mechanism by which it is absorbed (Gibaldi, 1971; Welling, 1977). The simultaneous ingestion of whole milk was shown to affect markedly the absorption of declomycin (Naggar and Daabis, 1980) and of nalidixic acid (Darwish et al., 1980), while milk intake had no appreciable influence on the extent of absorption of phenylbutazone (Loo et al., 1977). Most of the penicillins fall into the category of drugs whose absorption may be reduced by food (Welling et al., 1977). Examples of other drugs which may undergo either reduced or delayed absorption by food include cephalosporins (Harvengt et al., 1973), furosemide (Kelly et al., 1974), propantheline (Gibaldi and Grundhofer, 1975) and diazepam (Naggar and Daabis, 1980). A controlled study correlating specific dietary components with effects on acetaminophen absorption showed that pectin, present in high amounts in certain meals, may delay drug absorption through adsorption or increase in the viscosity of the gastrointestinal content (Jaffe et al., 1971). Food containing signifi-

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cant amounts of divalent metal ions was reported (Jaffe et al., 1971) to inhibit absorption of tetracyclines at least partially by a chelation mechanism. On the other hand, the absorption of tetracycline has been shown to increase in the presence of the neutral fat tripalmitin, an effect probably associated with removal of calcium ions (De Marco and Levine, 1969). A high-lipid breakfast also increased the absorption of griseofulvin, due to its extremely lipophilic character (Kabasakalian et al., 1970). Food, decreasing intestinal transit rate, improved the absorption of riboflavin 5-phosphate, an effect consistent with a site-specific saturable absorption mechanism (Jusko and Levy, 1967). In case of nitrofurantoin, a similar effect was rationalized in terms of delayed stomach emptying, permitting more drug to dissolve in the stomach before it passes into the optimal absorption environment of the small intestine (Macheras and Reppas, 1986b). Ketoprofen, a widely used anti-inflammatory agent, is normally given to patients with milk or food to minimize gastrointestinal irritation. Its bioavailability was recently shown to be significantly affected by the coadministration of aluminium hydroxide (Ismail et al., 1987). Since much emphasis has been placed on whether or not drugs should be ingested with meals, the need for information on the influence of milk and of a standard breakfast on ketoprofen bioavailability was deemed necessary.

Materials and Methods

Profenid capsules containing 50 mg of ketoprofen, manufactured by Alexandria Pharmaceutical Co., Alexandria, Egypt, under licence from Rhone Poulenc, Paris, France, were purchased locally (batch number 40802).

Bioavailability study

The subjects who participitated in this study were 4 adults, 3 males and one female, healthy and capable of informed consent. Their ages ranged from 22 to 42 years and their weights from 60 to 75 kg. After an overnight fast, one profenid capsule was swallowed with 250 ml of water (treatment A) or 250 ml of whole skim milk (treatment B) in the fasting condition; or with 250 ml of water immediately after a standard breakfast (treatment C). This breakfast, very common in Egypt, consisted of 60 g boiled egg, 130 g wholemeal bread, 20 g of processed cheese containing 40% fat and 200 g of beans freed from water of boiling and well mixed with 20 g cottonseed oil and 5 ml of lemon juice. At least one week elapsed between treatments. The subjects were required to drink 250 ml of water after each void to assure an adequate volume of urine. They also abstained from eating or drinking other fluids for 4 h after drug administration and for two more hours they abstained from drinking tea or coffee to avoid a diuretic effect. Urine was collected at 0, 1, 2, 3, 4, 6, 8, 12 and 24 h following drug intake. Volume of each urine sample and the pH of some of them, were recorded. The samples were kept frozen until analysis.

Urine samples were analyzed for ketoprofen (free and conjugated) by a precise and rapid HPLC method (Bannier et al., 1980) following extraction. The extraction procedure (Populaire et al., 1973) involved the addition of 0.5 ml 1 N NaOH to 0.2 ml urine sample for initial alkaline hydrolysis of the drug conjugates, followed by a cleansing extraction step with 8 ml diethyl ether (Prolabo, France). The tube was agitated for 5 min, centrifuged for another 3 min, then the organic phase was discarded. The drug was then extracted from acid medium (1 ml 1 N HCl) with 7 ml ethyl acetate (Reidel-De Häen, Seezle, Hannover, F.R.G.). An aliquot of the ethyl acetate layer (5 ml) was evaporated and the residue was dissolved in the mobile phase. Ten μl were injected onto a reversed-phase column (Perkin-Elmer RP-8 column). The mobile phase, consisting of 0.025 M phosphate buffer, pH 3.0, containing 50% acetonitrile (acetonitrile for chromatography, E. Merck, Darmstadt), was pumped at a flow rate of 1.3 ml/min. UV detection was carried out at 264 nm. Bumadizone calcium was used as internal standard (BYK Gulden, Pharmazeutika, Konstanz, F.R.G.), 20 μg being added to each urine sample and standard (1 ml each) before extraction. Retention times were 6.5 and 11 min for ketoprofen and internal standard, respectively. Recovered standards were prepared by spiking

control (drug-free) urine with ketoprofen to cover a concentration range of 10–50 μg/ml and processing them with the test samples. Recovery values were obtained by comparing peak heights of standards prepared in urine with peak heights of direct-on-the-column injection of the same amount of ketoprofen and internal standard.

Results and Discussion

Ketoprofen is almost completely excreted as glucoronide which is not likely to be affected in its elimination by urinary pH changes (Ismail et al., 1987). The cumulative amounts of free ketoprofen and its conjugate excreted for each volunteer and the average amount excreted, after the 3 treatments, are shown in Table 1. For treatment A, the average total % excretion of the administered dose after 24 h was 76.25% (with S.D. of $\pm$ 1.54). These results are consistent with previously reported ones. Ismail et al., (1987) reported excretion of 78.34 $\pm$ 3.8% of the orally administered 50 mg dose over a 24-h period in 5 volunteers.

A comparison of excretion rate profiles, among the 3 treatments, for each subject and for the mean, is shown in Fig. 1. The simultaneous ingestion of milk with ketoprofen resulted in a decreased level of excretion throughout the entire span of the test, in each of the 4 volunteers, compared to treatment A. Mean peak excretion was reached in about 2.25 and 3 h in treatment A and B respectively. However, the difference in peak excretion rate was not statistically significant (Table 1). On the other hand, the average % amount of ketoprofen ultimately excreted (24 h) dropped from 76.25% after treatment A to 55.92% after treatment B (Table 1), which means a significant reduction in the extent of drug absorption. As reflected from the coefficient of variation of % mean excretion, the uniformity of ketoprofen absorption was also affected in the presence of milk (Table 1). Milk has a complex structure, it is a fluid in which drugs may be distributed within different phases. Both the aqueous and the lipid phases may act as solvents, and adsorption on proteins is also possible (Macheras and Reppas, 1986a). If a rise in pH of the stomach fluid occurs due to the strong buffering capacity of milk (pH is about 6.8), it may increase both dissociation and dissolution of ketoprofen with a reported pK_a value around 5 (Ismail et al., 1987). Any rise in dissociation of this weakly acidic drug will impede its absorption, thus opposing, at least partly, any beneficial effect due to an eventual rise in dissolution rate. However, recent studies have shown that the rate of dissolution of drugs in milk is generally slow, especially under in vivo conditions (Macheras and Reppas, 1986b).

The statistical analysis of the results of treatment C (Table 1) shows that food had significantly altered the absorption pattern of ketoprofen. The time of peak excretion was shifted to 3.5 h and the mean peak excretion rate was significantly lowered. Fig. 1 shows that the amount of excretion after a standard breakfast was much depressed in the earlier time periods and was elevated slightly in the later ones. The food appears to cause a delay in absorption, extending it over a longer time period rather than permanently inhibiting absorption. However, there was a significant difference in the total % mean excretion between treatments A and C. Therefore, food significantly reduced both the rate and extent of ketoprofen absorption. Several factors might explain the inital reduction in ketoprofen absorption by food. The bulky and water-absorbing nature of some components of the breakfast, like beans and bran, present in bread, would decrease or delay absorption by decreasing the amount of biological fluids available in the gastrointestinal tract, and thereby reducing the dissolution rate of the drug from the capsule (Jaffe et al., 1971). This could be a rate-limiting factor in the absorption process, since ketoprofen is considered to be only very slightly water-soluble at the low pH values normally encountered in the human stomach. Ismail and coworkers (Ismail et al., 1987) reported a solubility of 15.3 mg% at pH 1.4. Food and viscous liquids like cottonseed oil also slow gastric emptying and intestinal transit. Moreover, increase in viscosity by food could possibly retard both the dissolution rate of ketoprofen and the diffusion of dissolved ketoprofen. Solid or semisolid food in this respect may act as a mechanical barrier preventing drug movement towards the mucosal

TABLE 1

Cumulative urinary excretion of ketoprofen (mg) obtained after the administration of a 50 mg capsule to fasting volunteers with water (treatment A) or milk (treatment B), and after standard breakfast (treatment C)

Time (h)	Treatment A					Treatment B					Treatment C				
	Volunteers				Mean (±S.D.)	Volunteers				Mean (±S.D.)	Volunteers				Mean (±S.D.)
	AE	ME	VN	MZ		AE	ME	VN	MZ		AE	ME	VN	MZ	
1	2.98	7.37	11.23	3.28	6.22 (7.13)	0.94	1.29	0.79	0.84	0.97 (0.38)	0.5	0.97	0.72	0.6	0.7 (0.34)
2	11.10	23.81	21.21	13.45	13.4 (11.8)	6.76	4.78	8.92	4.71	6.29 (3.57)	2.4	5.07	5.58	3.24	4.07 (2.90)
3	21.22	30.3	26.51	27.45	26.4 (5.64)	16.6	16.0	20.1	14.2	16.7 (3.87)	5.7	10.8	14.3	6.54	9.35 (7.44)
4	26.25	33.45	31.91	30.24	30.5 (5.12)	23.2	18.9	23.8	18.4	21.1 (5.65)	12.2	17.9	18.7	15.3	16.0 (5.30)
6	31.15	35.70	35.71	32.41	33.7 (4.53)	26.7	21.9	26.1	21.9	24.1 (5.16)	20.8	23.6	22.0	20.1	21.6 (2.78)
8	32.86	36.60	36.51	33.48	34.9 (3.91)	28.0	23.5	27.3	24.5	25.8 (4.17)	24.2	27.4	24.7	23.2	24.9 (2.89)
12	34.99	37.53	37.17	35.34	36.2 (2.52)	28.8	24.4	27.9	26.2	26.8 (3.48)	27.2	29.4	28.2	25.8	27.7 (2.66)
24	37.75	37.91	38.1	38.79	38.1 (0.77)	30.4	24.7	28.4	28.4	28.0 (3.75)	28.3	31.3	30.2	28.8	29.7 (2.57)

Values with paired Student's t-test: mean % excreted at 24 h (±S.D.) for A, 76.25%(1.54); for B, 55.92%(7.49); for C, 59.33%(5.14); $t = 8.48, P < 0.005$ for A and B; $t = 10.93, P < 0.005$ for A and C. Mean peak excretion rate(mg/h) (±S.D.) for A 12.95(5.25); for B, 10.42(1.77); for C, 7.43(3.01); $t = 1.86$, $0.05 < P < 0.1$ for A and B; $t = 3.2$, $P < 0.05$ for A and C. Coefficient of variation for mean % excreted at 24 h was 2%, 13.4% and 8.7% for treatments A, B and C, respectively.

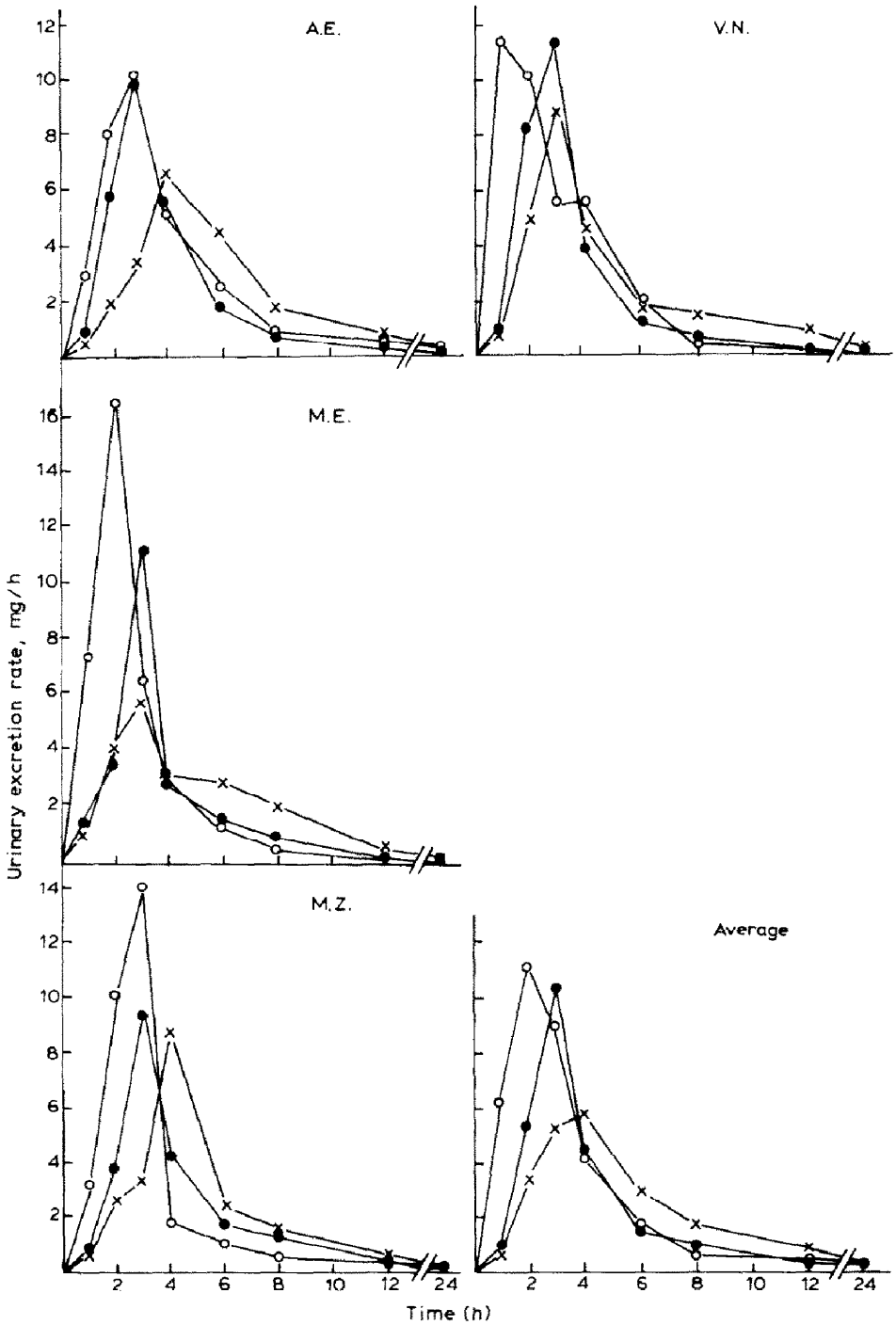

Fig. 1. Urinary excretion rate of ketoprofen following the administration of 50 mg of ketoprofen to volunteers with water (○——○) or milk (●——●) and after standard breakfast (×——×).

surface of the gastrointestinal tract (Gibaldi, 1971). Food may also influence drug absorption more directly because of adsorption onto food components like proteins in which beans are rich as well as cheese and eggs and like carbohydrates from bread (Welling, 1977). The process seems to be only partially reversible since the ultimate amount of drug absorbed is decreased. It is to be noticed that although the absorption of ketoprofen in the presence of food was slower than in the presence of milk, it was however more complete, based on the total % excretion. Moreover, the coefficient of variation was lower (Table 1). An explanation of these results may reside in the fact that prolonged residence in the stomach due to solid diets may allow more drug, than in case of milk, to dissolve slowly before passing to the duodenum. Previous studies showed that gastric emptying is much slower in presence of food than when about 250 ml of milk is administered (Macheras and Reppas, 1986b).

In conclusion, these results can lead to significant consequences relating to better drug efficacy and safety. In order to optimize dosage regimens to benefit ultimately the patient in terms of increased circulating drug levels and reduced gastrointestinal irritation, more data as to the influence of dietary components on ketoprofen bioavailability are still required.

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