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The Effect of Food on the Systemic Availability of Ketoprofen

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Summary. We have studied the pharmacokinetics of ketoprofen, a non-steroidal anti-inflammatory drug, in 12 patients after a single 100 mg oral dose both in fasting conditions and with a meal. Food significantly affected the peak plasma concentration of ketoprofen and decreased its absorption rate. However, the extent of absorption of ketoprofen, as reflected by the area under the plasma concentration time curve, appeared to be unchanged in the presence of food.

Key words: ketoprofen; food, bioavailability

Ketoprofen, a phenylpropionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of inflammatory or degenerative rheumatic diseases. Patients are often recommended to take ketoprofen with a meal in order to improve its gastric tolerance [1]. Previous studies have investigated the influence of food on the absorption of enteric-coated ketoprofen [2] or the effect of meal size and composition on the systemic availability of a sustained-release pellet formulation [3]. The present study on the effect of food on ketoprofen pharmacokinetics was conducted with conventional hard gelatin capsules containing crystalline powder of ketoprofen.

Patients and Methods

We studied twelve adults (11 men and 1 woman), 34 to 60 years old (mean ± SD: 47 ± 10 years) and ranging in body weight from 60 to 95 kg (72 ± 10 kg). They were hospitalized for sciatica, all had normal hepatic and renal function and all give their informed consent.

Each subject was given two capsules, each containing 50 mg ketoprofen (Profénid, Laboratoire SPECIA), with 100 ml of water on two occasions, three days apart : during fasting conditions (Treatment A) and with a standardized meal (Treatment B). Before each test the patients abstained from food and liquids for 10 h. The standard meal consisted of grilled meat, vegetables, cheese, fruit, bread, and water (950 kCal, 35% lipid, 50% carbohydrate, and 15% protein). No food or drink other than those stated as part of the treatment was ingested during the 4 h after taking the drug. After that time a normal diet was allowed.

Blood samples were collected before drug administration (0 h) and at 15, 30, and 45 min and 1, 1.25, 2, 3, 4, 8, 12, and 24 h after drug ingestion during Treatment A, and at 30 min and 1, 1.25, 1.75, 2, 2.50, 3, 4, 8, 12, and 24 h after drug ingestion during Treatment B. After centrifugation the plasma was frozen and stored at −20 °C until assayed.

Plasma concentrations of ketoprofen were measured by a specific and sensitive high performance liquid chromatographic method. The inter-assay precision over the 10 $ng \cdot ml^{-1}$ -20 $\mu g \cdot ml^{-1}$ plasma concentration range varied from 3 to 1%. Full details of this method have been published [4].

The following variables were calculated:
- the peak concentration (C_{max}) and the time to peak concentration (t_{max}),
- the area under the plasma concentration time curve from 0 to infinity (AUC),
- the mean residence time (MRT), which was determined according to the formula [5]

$$MRT = \frac{AUMC}{AUC} = \frac{\int_0^\infty t\,C\,(t)dt}{\int_0^\infty C\,(t)dt}$$

where AUMC is the area under the first moment curve
- the elimination rate constant (λ_z)
- the apparent total plasma clearance after oral dosing (CL/f), which was determined by the ratio of the dose (D) to the AUC
- the apparent volume of distribution at steady-state (V_{ss}/f), which was determined from the equation [6]

$$\frac{V_{ss}}{f} = D \times \frac{AUMC}{AUC^2}$$

The calculation of these variables was achieved by interpolation through a third degree Lagrange polynomial [7] and monoexponential extrapolation to infinity based on the four last kinetic values. The extrapolated part represented less than 0.017 of the AUC and less than 0.13 of the AUMC.

The Wilcoxon matched test at the $p<0.05$ significance level was used to compare within-patient differences for Treatments A and B.

Table 1. Pharmacokinetics of ketoprofen after a single 100 mg oral dose in the absence (A) and presence (B) of food. The data are given as mean ± SD or median (range)

Variable	During fast (Treatment A)	During meal (Treatment B)	Wilcoxon matched test
C_{max} ($\mu g \cdot ml^{-1}$)	9.09 ± 2.55	6.07 ± 3.20	$p=0.023$[a]
t_{max} (h)	0.98 (0.50 – 2.06)	2.42 (0.83 – 7.32)	$p=0.004$[a]
λ_z (h^{-1})	0.16 ± 0.07	0.17 ± 0.05	$p=0.515$
AUC ($h \cdot \mu g \cdot ml^{-1}$)	18.4 ± 6.0	16.6 ± 4.8	$p=0.583$
MRT (h)	3.74 ± 0.94	5.24 ± 1.71	$p=0.006$[a]
CL/f ($l \cdot h^{-1}$)	5.93 ± 1.80	6.44 ± 1.58	$p=0.374$
V_{ss}/f (l)	1.47 ± 1.12	2.43 ± 1.22	$p=0.050$

[a] Statistically significant, $p<0.05$

Results and Discussion

The mean values of the kinetic variables and the results of the statistical analysis are summarized in Table 1. The plasma concentration time curve from one of the patients is shown in Fig. 1. The pharmacokinetic variables found in this study in fasting conditions are in agreement with those reported previously [8, 9].

When individual data were compared for a given subject, it appeared that a substantial meal significantly affected the peak concentration of the drug and its absorption rate, as reflected by the time to reach peak concentration. Although ketoprofen, an acidic compound, may be absorbed directly from the stomach, its optimal site for absorption is in the small intestine [10]. The delay in gastric emptying induced by concomitant food consumption might thus explain the reduced absorption rate. However the AUC, reflecting the extent of absorption, was unchanged in the presence of food. Similar results have been reported for other NSAIDs [1, 8, 10] and for other formulations of ketoprofen [2, 3].

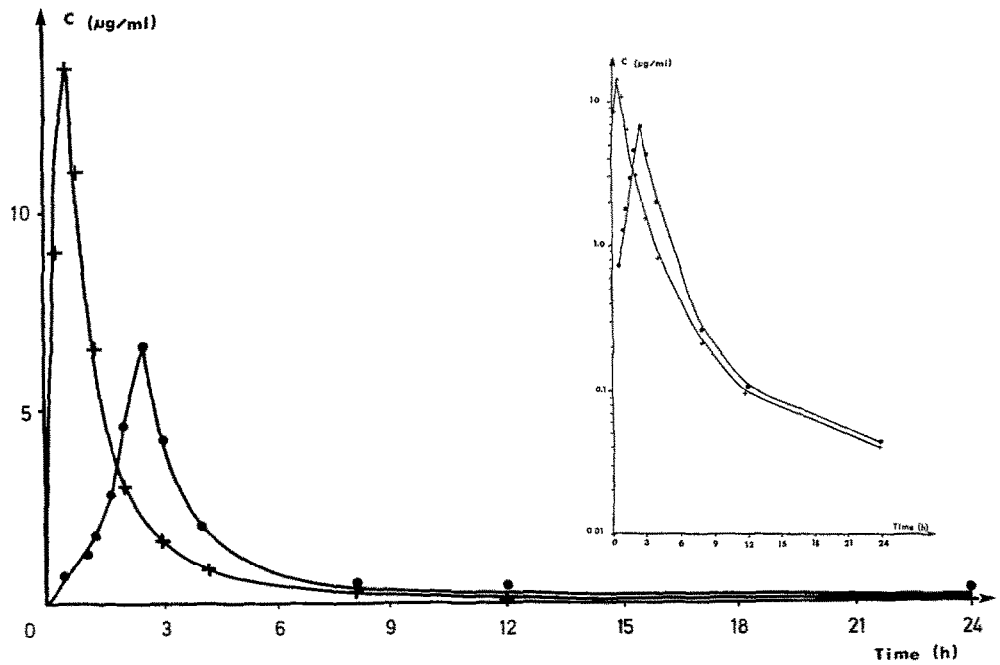

Fig. 1. Plasma concentration-time profiles in one patient after the oral administration of single 100 mg doses of ketoprofen during a complete fast (+) and during a standard meal (●). *Inset:* Semi-log plot

The delayed absorption of ketoprofen might explain the increase of MRT in Treatment B as compared with the fasting condition. This hypothesis is supported by the fact that the elimination rate constant, and the apparent total plasma clearance were constant in the fasted and fed states. Indeed, the MRT is a composite variable which describes all kinetic processes of the drug in the body, including absorption and disposition [11].

Whether there is a correlation between the plasma concentration and the therapeutic effect of NSAIDs in rheumatic patients is questionable [12], and it has never been reported that the clinical efficacy of ketoprofen is related to any of its pharmacokinetic characteristics. However, since NSAIDs such as ketoprofen are usually given in multiple doses, and since the AUC of ketoprofen is not affected by food intake, the changes in C_{max} and t_{max} should not be considered of clinical importance, unless the drug is indicated for acute pain.

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