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Influence of gastric acid secretion blockade and food intake on the bioavailability of a potassium diclofenac suspension in healthy male volunteers

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Abstract. The bioavailability of a single dose of a potassium diclofenac (KDIC) suspension (Flogan, Merck, 7ml, 105 mg) was studied in 13 healthy male volunteers in the fasting state (placebo phase, PLA), after gastric acid secretion blockade (subacute pretreatment with omeprazole, OME phase) and after food intake (FOOD phase). A 14-day washout period between phases was adopted. Serum samples were obtained over a 24 hour interval and the diclofenac concentrations were determined by high pressure liquid chromatography with ultraviolet detection. From the serum diclofenac concentration vs time curves, the $AUC_{[0-\infty]}$ (area under the concentration vs time curves from 0 to infinity), C_{max} (maximum achieved concentration), t_{max} (time to achieve C_{max}), K_e (terminal first order elimination constant), half-life values ($t_{1/2}$) and $AUC_{[0-\infty]}/t_{1/2}$ ratio as an index of diclofenac clearance, were obtained. All these variables were analyzed using both parametric and non-parametric statistics. In the presence of food, KDIC absorption was delayed (as shown by lower C_{max} and greater t_{max} values) and decreased (as shown by lower $AUC_{[0-\infty]}$ values), and the serum diclofenac concentration vs time curves showed a biphasic pattern. Omeprazole pretreatment did not change the absorption parameters. Both of these treatments altered the diclofenac clearance, as assessed by the $AUC_{[0-\infty]}/t_{1/2}$, $t_{1/2}$ and K_e values, although the changes were not considered to be clinically significant, because of the wide therapeutic range for diclofenac. The delay in the rate of diclofenac absorption produced by food intake was not due to an increase in the gastric pH, and could be of particular importance when rapid analgesia is desired.

Key words: potassium diclofenac suspension – human volunteer pharmacokinetics – bioavailability – gastric acid blockade – omeprazole – food intake – drug interaction

Introduction

Diclofenac ([2-(2,6-dichloroanilino)phenyl]acetic acid) is a potent nonsteroidal antiinflammatory drug (NSAID) belonging to the phenyl acetic group, and is widely used in its sodium salt form in cases of chronic and acute inflammation [Altman 1986, Calabro 1986, Kantor 1986, Zuckner 1986]. The potassium salt of diclofenac (KDIC) has been marketed mainly in Latin America and has been prescribed for acute conditions to provide fast analgesic and antiinflammatory effects [Bahamonde and Saavedra 1990, Verstraeten and Bakshi 1991].

The main problem associated with NSAID therapy is the ability of these drugs to induce gastrointestinal injury, most notably gastric ulceration, bleeding and perforation, as well as an increased risk of bleeding from preexisting peptic ulcers [Soll et al. 1991]. In an attempt to reduce NSAID-induced mucosal lesions and ulcer formation or exacerbation, several clinical practices have been adopted including the oral administration of the drug at mealtimes, the use of special preparations such as enteric-coated tablets or the concomitant administration of antacids [Brzozowski et al. 1993], histamine H_2 receptor antagonists [Van Berge Henegouwen and Smout 1991], prostanoids [Miller 1992] or proton-pump inhibitors [Scheiman et al. 1994].

Drugs dissolved in biological fluids exist as predominantly weak ionizable species and are absorbed across the plasma membrane in their nonpolar or unionized forms. The ionized forms cannot cross the membrane due to the hydrophobic nature of the latter. Consequently, the pH of the microenvironment is critical in determining movement across the membrane [Wilson et al. 1989].

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The major physiological stimulus for acid secretion in the stomach is the ingestion of food, especially if the meal has a high protein content which possesses the greatest buffering capacity. The buffering action of food usually produces a temporary increase in gastric pH [Wilson et al. 1989]. Furthermore, the presence of food may influence the absorption of several drugs and can either enhance, delay or reduce their uptake thereby changing their bioavailabilities [Toothaker and Welling 1980].

Omeprazole is a proton-pump inhibitor and a potent blocker of basal gastric acid secretion, thus increasing the gastric pH. This drug therefore represents a therapeutic option for the treatment of certain peptic acid disorders [Lampkin et al. 1990].

Since KDIC can be clinically co-administered with the proton-pump inhibitor omeprazole and/or with food intake, pharmacokinetic interactions which could affect the bioavailability of diclofenac may occur.

In this study, we have compared the pharmacokinetics of a KDIC suspension in healthy male volunteers in the fasting state (placebo phase, PLA), after gastric acid secretion blockade (attained by subacute pretreatment of the volunteers with omeprazole, OME phase) and after food intake (FOOD phase).

Subjects, material and methods

Clinical protocol

Thirteen healthy male volunteers aged between 21 and 47 years (mean ± SEM: 29.4 ± 6.3 yr) and weighing 55 to 95 kg (mean ± SEM: 77.5 ± 10.1 kg) were selected for the study. The volunteers were free from significant cardiac, hepatic, renal, pulmonary, gastrointestinal, neurological and hematological diseases as determined within 4 weeks before the start of the study, by medical history, physical examination and laboratory screenings: for fasting blood glucose, urea, creatinine, AST, ALT, total bilirubin, total protein, serum albumin, alkaline phosphatase, sodium, potassium, chloride, uric acid, urinalysis, hemoglobin, hematocrit, total and differential white blood cell counts. All the volunteers gave their written informed consent to participate in the study, and the clinical protocol was approved by the Ethics Committee of the university hospital.

The study had a 3-stage design with a 14-day washout period between treatments. During each stage, the volunteers were hospitalized at 09:00 p.m. having already had a regular evening meal. After an overnight fast they received 105 mg of KDIC as a suspension (Flogan).

Gastric acid secretion blockade was achieved by administering omeprazole (Losec, 20 mg/day, p.o, as a single dose, for 5 days prior to hospitalization). Placebo was administered in the same manner as described for omeprazole.The efficacy of the treatment was assessed by measuring the pH of the gastric juice (collected via an intragastric cannula) before the first administration of either placebo or Losec and then before KDIC administration. This part of the study (administration of placebo and Losec) was carried out in a double-blind manner.

The influence of food intake on the pharmacokinetics of KDIC was assessed by comparing the pharmacokinetic profile after a standard breakfast with the placebo profile. The standard breakfast was composed of one sandwich consisting of 2 slices of bread (~40 g) and 2 slices of cheese (~30g), 1 cup of whole milk (~250ml), and 2 pieces of papaya (~250g).

Blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hours after KDIC administration, and the serum diclofenac concentrations were determined by reversed-phase HPLC with ultraviolet detection as previously described [Mendes et al. 1994].

Pharmacokinetic and statistical analysis

The maximum observed serum concentration (C_{max}) and the time required for this to be reached (t_{max}) were obtained from the drug concentration vs time curves. The terminal elimination rate constant (K_e) was estimated by the least square regression of the points describing a terminal log-linear decay phase. The half-life values ($t_{1/2}$) were derived from K_e where $t_{1/2} = \ln 2/K_e$. The areas under the diclofenac concentration vs time curves from 0 to 24 h ($AUC_{[0-24]}$) were calculated using the trapezoidal method, and from 0 to infinity ($AUC_{[0-\infty]}$) were calculated using the trapezoidal method up to the time at which the serum diclofenac concentration was above the detection limit of the method (10 ng/ml), and posterior addition of the value C/K_e (C: last detectable diclofenac concentration). An estimate of diclofenac clearance was made using the method of Schall et al. [1994], and consisted of the calculation of the ratio $AUC_{[0-\infty]}/t_{1/2}$.

The obtained pharmacokinetic parameters were expressed as geometric means with their respective 90% confidence intervals, except for t_{max} for which the arithmetic mean was determined. Individual ratios were statistically analyzed using both parametric (one-way ANOVA for ln-transformed data) and non-parametric methods [Hauschke et al. 1990], with the exception of t_{max}, where individual non-transformed differences were analyzed.

The assessment of bioequivalence as defined by Steinijans et al. [1991] was also used to determine whether a pharmacokinetic interaction had taken place. The bioequivalence range for the individual ratios of the ln-transformed variables was defined as 0.8 – 1.25.

Pharmaceuticals

The commercial KDIC suspension Flogan (7 ml equivalent to 105 mg KDIC) is marketed by Merck S.A. Ind. Quím., RJ, Brazil, and omeprazole (Losec, 20 mg tablet) by Merrel Lepetit Farm. Ind. Ltda., SP, Brazil.

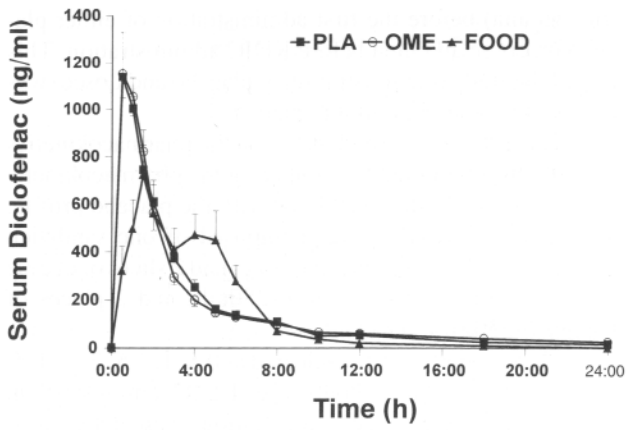

Fig. 1 Serum diclofenac concentration (mean ± SEM) versus time curves obtained in 13 healthy male volunteers following a single administration of 105 mg KDIC (7 ml of Flogan suspension) after placebo (PLA), gastric acid secretion blockade (OME) and food intake (FOOD)

Table 1 Mean KDIC pharmacokinetic parameters obtained in 13 healthy male volunteers after the ingestion of 105 mg KDIC (7 ml of Flogan suspension) under different conditions. PLA, placebo; OME, omeprazole; FOOD, food intake; CI, confidence interval

Parameter	PLA	OME	FOOD
$AUC_{[0-24]}$ (ng h ml^{-1})			
Geom. mean	3,459	3,564	3,114
90% CI	2,987 – 4,005	3,186 – 3,986	2,617-3,706
$AUC_{[0-\infty]}$ (ng h ml^{-1})			
Geom. mean	3,502	3,644	3,114
90% CI	3,007 – 4,078	3,246 – 4,092	2,617-3,707
$AUC_{[0-\infty]}/t_{1/2}$			
Geom. mean	1,897	1,643	2,023
90% CI	1,578 – 2,282	1,331 – 2,029	1,528 – 2,678
C_{max} (ng/ml)			
Geom. mean	1,330	1,276	1,052
90% CI	1,084 – 1,631	1,136 – 1,435	827-1,338
K_e (h^{-1})			
Geom. mean	0.37	0.32	0.45
90% CI	0.29 – 0.47	0.26 – 0.39	0.37 – 0.55
$t_{1/2}$ (h)			
Geom. mean	1.95	2.21	1.54
90% CI	1.55 – 2.47	1.80 – 2.71	1.26 – 1.88
t_{max} (h)			
Median	0.5	0.5	3.0
Range	0.5 – 4.0	0.5 – 1.0	0.5 – 5.0

Results

Diclofenac and omeprazole were well-tolerated at the administered doses and no adverse effects were reported. After omeprazole treatment, the gastric juice pH was significantly increased from 1.67 ± 0.11 (PLA phase) to 6.90 ± 0.13 ($p < 0.01$, $n = 13$; Student's paired t-test).

Figure 1 shows the mean serum diclofenac concentration vs time curves for the PLA, OME and FOOD phases. The major mean pharmacokinetic parameters derived from the serum diclofenac concentration vs time curves are presented in Table 1.

Parametric and non-parametric analysis of individual $AUC_{[0-\infty]}$, C_{max} percentual ratios and t_{max} differences between OME and PLA phases did not show any statistically significant differences, as shown by their inclusion in the 80 – 125% interval (Table 2). However, the diclofenac clearance index $AUC_{[0-\infty]}/t_{1/2}$, as well as K_e and $t_{1/2}$ were altered by the subacute treatment with omeprazole (Table 2a).

FOOD treatment altered the diclofenac pharmacokinetics, as shown by the non-inclusion of the individual $AUC_{[0-\infty]}$, C_{max}, $AUC_{[0-\infty]}/t_{1/2}$, K_e and $t_{1/s}$ percentual ratios from the 80 – 125% interval, and the individual t_{max} differences (Table 2b).

Discussion

Omeprazole, like diclofenac, is biotransformed in the organism [Stierlin et al. 1979, Gugler and Jensen 1985]. Apart from its inhibitory activity on proton-pump and gastric acid secretion [Lampkin et al. 1990, Scheiman et al. 1994], omeprazole may also alter drug pharmacokinetics since it inhibits hepatic microsomal enzyme activity [Rogerson et al. 1977]. Omeprazole prevents the metabolism of diazepam and phenytoin by inhibiting this enzyme system [Gugler and Jensen 1985] and this effect could account for the decrease observed in diclofenac clearance, and the consequent increase in $t_{1/2}$ (Table 2a).

Another mechanism by which omeprazole affects drug pharmacokinetics is by altering drug absorption. For instance, omeprazole increases the absorption of bismuth from tripotassium dicitrate bismuthate [Treiber et al. 1994]. Diclofenac is a weak acid ($pK_a = 4.0$) and very liposoluble (partition coefficient n-octanol/buffer, pH 7.4 = 13.4), and could be well absorbed in the low pH of the stomach. Although omeprazole significantly increased the gastric pH (from 1.67 to 6.90), it did not affect the diclofenac $AUC_{[0-\infty]}$, C_{max} and t_{max}, indicating that gastric pH does not alter diclofenac absorption.

The administration of the KDIC suspension in the presence of food delayed the rate of diclofenac absorption (as shown by the greater t_{max} values). Thus, KDIC should not be administered with food when rapid analgesia is desired. Food administration also reduced the absorption of diclofenac (as shown by the lower C_{max} and $AUC_{[0-\infty]}$ values) and changed the absorption pattern. However, because of the wide therapeutic range for diclofenac, the latter finding probably has little or no clinical relevance. Al-

Table 2a Statistical analysis of the intergroup $AUC_{[0-\infty]}$, $AUC_{[0-\infty]}/t_{1/2}$, C_{max}, K_e and $t_{1/2}$ individual ratios and t_{max} individual differences for KDIC. PLA, placebo; OME, omeprazole; FOOD, food intake. CI, confidence interval. (*) According to Hauschke et al. [1990]. (**) Arithmetic mean

OME/PLA	Parametic		Non-Parametric*	
	Geom. mean	90% CI	Point estimate	90% CI
$AUC_{[0-\infty]}$				
% Ratio	104.1	90.5 – 119.7	103.3	89.4 – 122.7
$AUC_{[0-\infty]}/t_{1/2}$				
% Ratio	86.6	68.4 – 109.7	85.9	67.8 – 109.2
C_{max}				
% Ratio	96.0	80.2 – 115.0	96.8	78.1 – 115.8
K_e				
% Ratio	85.4	67.9 – 107.4	86.6	67.2 – 112.1
$t_{1/2}$				
%Ratio	113.5	79.8 – 161.3	99.5	76.3 – 164.6
t_{max}				
Difference (h)	–0.42**	–0.93 – – 0.08	–0.25	–0.5 – 0.0

Table 2b

FOOD/PLA	Parametric		Non-Parametric*	
	Geom. mean	90% CI	Point estimate	90% CI
$AUC_{[0-\infty]}$				
% Ratio	88.9	75.6 – 104.6	88.5	74.9 – 106.7
$AUC_{[0-\infty]}/t_{1/2}$				
% Ratio	106.6	76.3 – 149.0	107.8	76.9 – 148.3
C_{max}				
% Ratio	79.1	56.7 – 110.4	80.4	54.3 – 111.0
K_e				
% Ratio	120.1	88.2 – 163.6	120.1	87.2 – 165.1
$t_{1/2}$				
% Ratio	78.8	57.2 – 108.6	75.1	56.1 – 100.5
t_{max}				
Difference (h)	1.8**	0.8 – 2.8	1.8	0.8 – 2.5

though food in the stomach elevates gastric pH, other factors such as the viscosity of the stomach contents, gastric emptying rate and the volume of gastric secretions [Wilson et al. 1989] may also explain this observation.

The diclofenac clearance was decreased 13.4% by omeprazole and increased 6.6% by food intake. These changes were statistically significant since the 90% CI for individual $AUC_{[0-\infty]}/t_{1/2}$ percentual ratios were not included in the 80 – 125% range (Steinijans et al. 1991). Since an important overlap with the equivalence range was detected, these changes may reflect intersubject variation rather than true pharmacokinetic interaction. In any case, we feel they are too discrete to be of potential clinical significance.

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