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PHARMACOKINETIC INTERACTION BETWEEN FLURBIPROFEN AND ANTACIDS IN HEALTHY VOLUNTEERS*

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ABSTRACT

Gastrointestinal distress resulting from drug intake is often remedied by administering the drug with antacids. However, antacids have been shown to modify the absorption and excretion of many drugs. This study was designed to delineate the effects of aluminium and magnesium hydroxide antacid suspension (Maalox) on the pharmacokinetics of flurbiprofen. Since this drug is often used in the elderly, not only young healthy but also geriatric healthy male volunteers participated in the study. A group of twelve young and a group of seven geriatric volunteers received, in a crossover design, a single oral dose of 100 mg of flurbiprofen with and without Maalox. A non-stereospecific assay was used to determine the total (R+S enantiomers) of flurbiprofen in plasma. The relative pharmacokinetic parameters of total flurbiprofen determined from plasma samples were C_{max}, t_{max},k_{el}, $t_{1/2}$, and AUC_{∞}. The results indicate that the co-administration of Maalox with flurbiprofen had no effect on the rate and extent of total flurbiprofen absorption in young volunteers. In geriatric volunteers, the results indicate no effect of the antacid on the extent of drug absorption. There was a trend for lower plasma concentrations of total flurbiprofen with antacid in the geriatric group and hence a reduction in rate of flurbiprofen absorption although differences were not significant. The study also included a steady state determination of the influence of antacid administration on flurbiprofen pharmacokinetics. The group of young volunteers received, from Day 3 to Day 8, 100 mg of flurbiprofen every 12 h with and without Maalox. Steady state pharmacokinetics were similar to those after single administration: the antacid had no effect on either the rate or the extent of total flurbiprofen absorption.

KEY WORDS Flurbiprofen Antacids Interaction Steady state

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INTRODUCTION

Flurbiprofen (ANSAID®, The Upjohn Company) is an orally active, non-steroidal anti-inflammatory drug (NSAID) of the propionic acid classification. Flurbiprofen has been found to be efficacious in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondilytis.[1,2] Orally administered flurbiprofen is rapidly absorbed from the gastrointestinal tract. Peak serum concentrations occur 1–2h following drug administration and the terminal serum elimination half-life is approximately 5·5h.[3] The major metabolites of flurbiprofen are hydroxylation and methylation products. Between 20 and 25 per cent of the administered dose is excreted in the urine as unchanged flurbiprofen and 65 to 85 per cent of the unchanged drug and its metabolites are in the form of glucuronide and sulfate conjugates.[3,4] The extent of flurbiprofen binding to serum albumin is greater than 99 per cent.[4]

Like other NSAIDs of the 2-arylpropionic acid class, flurbiprofen is administered as a racemate mixture. However, its pharmacological properties are associated almost entirely with the S-enantiomer and a recent study shows that flurbiprofen does not undergo enantiomeric inversion either systemically or presystemically.[5]

The most commonly reported adverse effects with flurbiprofen belong to the category of gastrointestinal irritation.[1] Gastrointestinal distress from NSAIDs is often remedied by administering the drug with antacids. Antacids can affect the absorption and excretion of many drugs. Studies with other NSAIDs have indicated that antacid administration alters the absorption characteristics for indomethacin, diflunisal, and asprin.[6–8] Postulated mechanisms for the alteration of drug absorption characteristics include alteration of drug ionization by gastric pH changes, absorption or complexation of the drug, and modifications in gastric emptying rates.[9] Other investigations have shown no effect of antacid administration on the bioavailability of ibuprofen, ketoprofen, piroxicam, and tolmetin.[10–13]

Patients receiving flurbiprofen may also be taking antacids and the effects of antacids on the absorption of flurbiprofen have not been reported. Although the use of NSAIDs is often indicated in the elderly population suffering from rheumatoid diseases, the same lack of information is apparent concerning the influence of aging on the disposition of flurbiprofen. For these reasons, the objective of this study was to investigate the effect of aluminium and magnesium hydroxide antacid suspension on the pharmacokinetics of flurbiprofen in young and geriatric volunteers.

MATERIALS AND METHODS

Subjects

Twelve normal healthy male volunteers, aged 21 to 31 years, participated in the study; they are hereafter referred as to the young volunteers. The second

group of volunteers, referred as to the geriatric volunteers, consisted of seven healthy male volunteers, aged 58 to 77 years. Both groups gave a written informed consent before being included in the protocol. The subjects were selected for the study following a physical examination and assessment of laboratory values for serum chemistries, complete blood count, and urinalysis. Exclusion criteria included a history of hypersensitivity to flurbiprofen; history of any blood dyscrasia; history or presence of gastrointestinal ulcer or presence of dyspepsia; intake of alcohol, prescription or non-prescription drugs 1 week prior to the study; intake of any known metabolic enzyme inducers or inhibitors in the 4 weeks preceding the study.

Treatments

Each young subject received, according to a randomized crossover experimental design, two drug treatments. Treatment A was flurbiprofen 100 mg with concurrent antacid suspension (30 ml taken 30 min before the anti-inflammatory drug) and Treatment B was flurbiprofen alone. Both treatments were administered as a single oral dose on Days 1 and 8 and every 12 h for 10 doses on Days 3 through 7.

Each geriatric subject received, according to a randomized crossover experimental design, the same oral single drug treatments as the young volunteers (Treatment A and B). The geriatric volunteers were not submitted to a multiple dosage regimen.

Study drugs were supplied as flurbiprofen (ANSAID® Tablets, lot P-178, The Upjohn Company, 865 York Mills Road, Don Mills, Ontario) and aluminum and magnesium hydroxide suspension (Maalox, lot 25663, Rorer Inc. Fort Washington, PA). There was a 5-day washout period between treatment regimens.

Experimental protocol

Young and geriatric subjects fasted for at least 7 h prior to and for 5 h following the drug treatment administration at 7 am on Days 1 and 8. During the multiple dose portion of the study (Days 3 through 7), young volunteers took their breakfast and evening meal 90 min after drug administration which was at 7 am and 7 pm. All doses of flurbiprofen were taken with 240 ml of water. Adverse reactions were monitored throughout the study.

Plasma sampling

On Days 1 and 8 of each phase, blood samples were collected by venipuncture using vacutainers with EDTA (B–D 6457), just prior to dosing and at 0·33, 0·66, 1, 1·5, 2, 3, 4, 6, 8, 12, 16, 24, and 36 h following drug administration. The samples were centrifuged at 2000 rev min^{-1} for 20 min and the harvested plasma was frozen at –20° until assayed. Plasma concentrations were determined by

HPLC using a non-stereospecific method published by Albert *et al.*[14]. Total flurbiprofen was extracted from hydrochloric-acid acidified plasma with a pentane-ether (80:20) mixture; the extracted drug was then separated from other plasma constituents with an octadecylsilane column using a mobile phase of acetonitrile–water–phosphoric acid (650:350:0·5, v/v/v). A fluorescence detector with excitation at 250 nm and emission at 315 nm was used to monitor plasma levels; the sensitivity of the method is reported as 0·1 μg ml^{-1}.

Pharmacokinetic parameters

The following pharmacokinetic parameters were derived from total plasma flurbiprofen concentrations: C_{max}, t_{max}, k_{el}, $t_{½}$, and AUC_{∞}. The maximum total plasma flurbiprofen concentration (C_{max}) and the time to reach maximum plasma flurbiprofen concentration (t_{max}) were observed values. The apparent

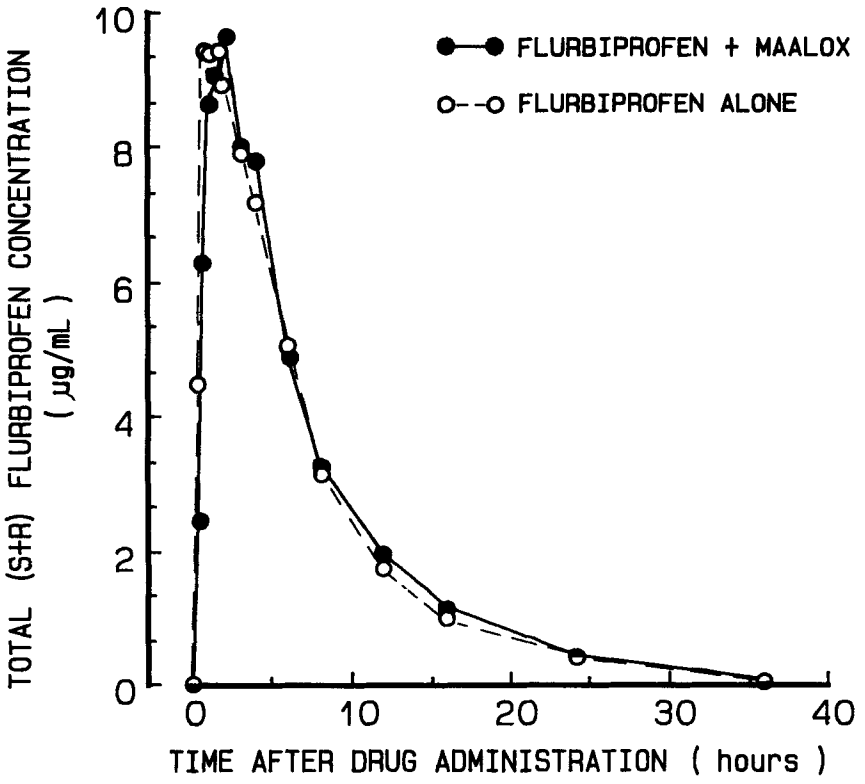

Figure 1. Mean plasma concentration–time profiles following the single dose administration of flurbiprofen 100 mg with (●) and without (○) Maalox in young healthy volunteers (n = 12)

elimination rate constant (k_{el}) was determined by a linear least squares regression analysis of the terminal log-linear portion of the concentration versus time curve. The areas under the plasma versus time curve (AUC) from zero to 36 h of Day 1 and 0 to t (where t is the dosing interval of 12 h) of Day 8 were determined by the trapezoidal rule. For the single dose portion of the study, AUC from 36 h to infinity was estimated by dividing the concentration at 36 h by k_{el}.

Statistical analysis

Evaluation of differences between treatments for AUC, C_{max}, t_{max}, and k_{el} were undertaken using a General Linear Model procedure of the Statistical Analysis System (Cary, NC, USA). The level of significance for all statistical tests was $p < 0{\cdot}05$. The power to detect a 20 per cent difference between treatments was determined for comparisons of AUC and C_{max}.

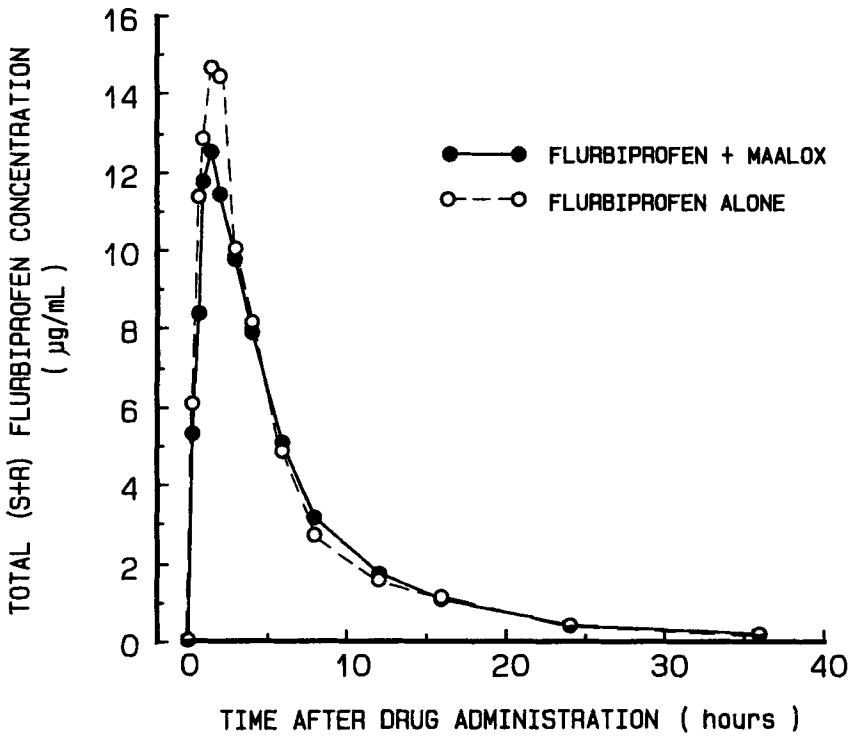

Figure 2. Mean plasma concentration–time profiles following the single dose administration of flurbiprofen 100 mg with (●) and without (○) Maalox in geriatric healthy volunteers ($n = 7$)

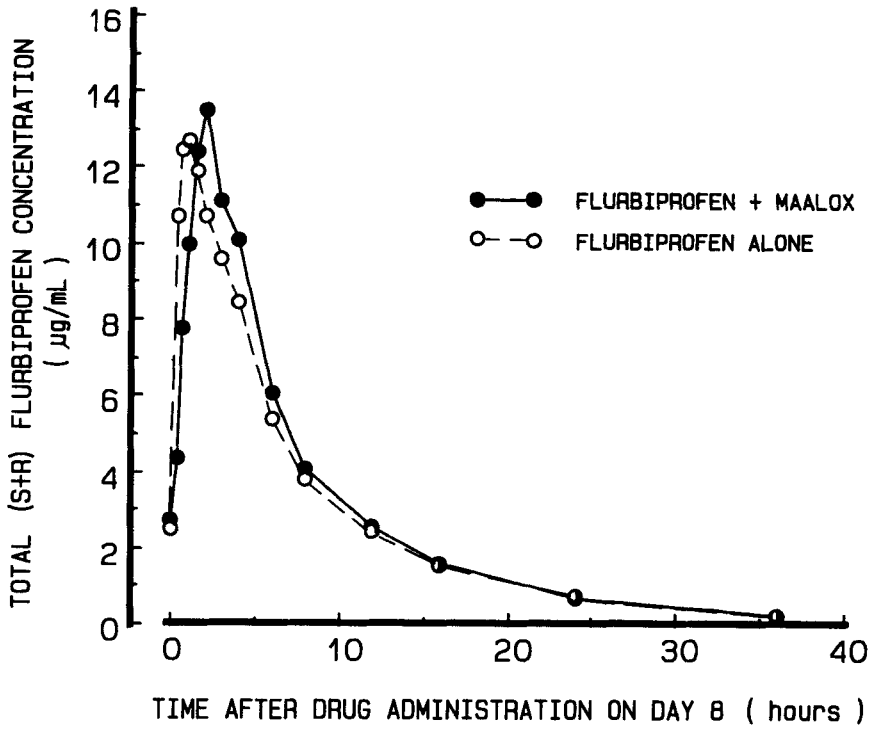

Figure 3. Mean plasma concentration–time profiles following the multiple dose administration of flurbiprofen 100 mg with (●) and without (○) Maalox in young healthy volunteers (n = 12)

RESULTS

The mean single dose total plasma flurbiprofen concentration versus time profiles with and without Maalox are shown in Figures 1 and 2, for young and geriatric volunteers, respectively. Figure 3 represents, in young volunteers, the mean steady state drug concentration curves after a twice a day administration of flurbiprofen with or without the antacid for 5 days.

The mean pharmacokinetic data for single dose conditions are given in Tables 1 and 2, for young and geriatric volunteers, respectively. As can be observed from Table 1, the co-administration, to young volunteers, of Maalox with flurbiprofen had no effect on the rate and extent of flurbiprofen absorption, since neither the C_{max} or t_{max} nor the AUC_∞ were modified. In the geriatric healthy volunteers (Table 2), the extent of flurbiprofen absorption was not affected by the co-administration of Maalox since the AUC_∞ was not modified. However, the rate of drug absorption was slightly although not significantly modified by the antacid; the C_{max} was 13·3 and 18·3 $\mu g\ ml^{-1}$ with and without Maalox, respectively. The time to reach maximum plasma concentration was also modified: it was 1·9 h with Maalox and 1·5 h without Maalox.

Table 1. Flurbiprofen pharmacokinetic values (mean ± SD) following single dose administration (100 mg) to young volunteers

	Flurbiprofen + Maalox	Flurbiprofen
C_{max} ($\mu g\ ml^{-1}$)	12·2 ± 3·1	12·6 ± 3·1
t_{max}(h)	1·9 ± 1·1	2·0 ± 1·7
k_{el} (h^{-1})	0·14 ± 0·03	0·14 ± 0·02
$t_{1/2}$ (h)	5·1*	5·0*
AUC_∞ ($\mu g.h\ ml^{-1}$)	78·1 ± 23·1	76·6 ± 21·2

*Expressed as the harmonic mean.

Table 2. Flurbiprofen pharmacokinetic values (mean ± SD) following single dose administration (100 mg) to geriatric volunteers

	Flurbiprofen + Maalox	Flurbiprofen
C_{max} ($\mu g\ ml^{-1}$)	13·3 ± 1·8	18·3 ± 5·6
t_{max} (h)	1·9 ± 1·1	1·5 ± 0·6
k_{el} (h^{-1})	0·12 ± 0·06	0·11 ± 0·04
$t_{1/2}$(h)	5·8*	6·5*
AUC_∞ ($\mu g.h\ ml^{-1}$)	85·1 ± 20·6	90·2 ± 23·5

*Expressed as the harmonic mean.

Table 3. Flurbiprofen pharmacokinetic values (mean ± SD) under steady state conditions in young volunteers

	Flurbiprofen + Maalox	Flurbiprofen
C_{max} ($\mu g\ ml^{-1}$)	16·2 ± 3·8	16·2 ± 4·4
t_{max} (h)	1·9 ± 1·0	1·6 ± 1·5
AUC_{0-t} ($\mu g.h\ ml^{-1}$)	80·7 ± 19·6	76·8 ± 19·1

The mean pharmacokinetic data under steady state conditions are given in Table 3. As can be seen from this table, no differences were detected in any of the pharmacokinetic parameters under study. These results thus indicate that the co-administration of Maalox with flurbiprofen had no effect on the extent and rate of total drug absorption in multiple dose regimens.

Adverse effects reported were rash, dyspepsia, pain, edema, and diarrhea. All adverse effects were transient and all subjects completed the study.

DISCUSSION

In this study, the administration of aluminum and magnesium hydroxide antacid suspension had no effects on the pharmacokinetics of total (S+R)

flurbiprofen under single dose or multiple dose conditions in young volunteers. No significant differences were detected between treatments for the extent (AUC_∞) and rate of flurbiprofen absorption (C_{max}, t_{max}). The lack of a significant difference for k_{el} indicates that the elimination of flurbiprofen was not altered by the antacid administration.

A power analysis indicated that there was a 99·9 per cent probability of detecting a 20 per cent difference in means for AUC_∞ at $a = 0{\cdot}05$. Under the same detection conditions, the power values for C_{max} (single dose) and C_{max} (steady state) were 64·7 per cent and 42·6 per cent, respectively. The results indicate that the observed inter-subject variability was greater for C_{max} than AUC_∞.

At steady state, AUC_{0-t} are 80·7 and 76·8 μg.h ml^{-1} with and without Maalox, respectively. These values are not significantly different from AUC_∞ of 85·1 and 90·2 μg.h ml^{-1} with and without Maalox obtained under single dose conditions. These results indicate that steady state conditions for each treatment had been achieved using the described dosing regimen.[15] The accumulation in the body with this dosing regimen was estimated using equation (1)[15]

$$R = \frac{(C_{ss})\text{min}}{(C_1)\text{min}} \qquad (1)$$

where R is the accumulation ratio, $(C_{ss})_{min}$ is minimum plasma flurbiprofen concentration at steady state and $(C_1)_{min}$ is the minimum plasma flurbiprofen concentration following the first dose. The accumulation ratio was 1·42 for flurbiprofen 100 mg every 12 h given with or without the antacid.

However, it is worth noting that a non-stereospecific method of analysis was used to analyse plasma samples and therefore total flurbiprofen (S+R isomers) was measured. Since a recent study[5] showed that flurbiprofen does not undergo enantiomeric conversion in man and that similar kinetic profiles were obtained for individual isomers, the use of a stereospecific assay in this study may have led to similar results.

The results of this investigation are similar to those reported for ibuprofen[11] and ketoprofen.[12] These findings suggest that aluminium and magnesium hydroxide antacid suspension does not alter the pharmacokinetics of NSAIDs of the propionic acid class.

In conclusion, the results of this study indicate that concurrent aluminum and magnesium hydroxide suspension administration with flurbiprofen does not affect the pharmacokinetics of total flurbiprofen under single dose or steady state condition in young volunteers. They also indicate that the antacid does not produce any effect on the extent of total drug absorption in geriatric volunteers. There was a trend for lower maximum plasma concentrations of total flurbiprofen and increased time to reach this concentration with antacid administration in the geriatric group. However, the antacid did not significantly alter the rate of total flurbiprofen absorption in this group.

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