UNALTERED IBUPROFEN-INDUCED FAECAL BLOOD LOSS UPON COADMINISTRATION OF MOCLOBEMIDE

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SUMMARY

The influence of moclobemide on ibuprofen-induced faecal blood loss was investigated in 24 volunteers. The subjects were randomly assigned to one of two groups and received from day 1 until day 14 either moclobemide 150 mg t.i.d. (group A) or placebo t.i.d. (group B). On days 8-14, when moclobemide concentrations in group A were at steady state, all volunteers additionally received ibuprofen (600 mg t.i.d.). From day 15 to 21, all subjects received placebo alone. Faecal blood loss (FBL) was quantified daily by the ^{51}Cr-labelled erythrocyte method.

As expected for ibuprofen, a significant increase in FBL during the second week of the study was observed. There was no difference in FBL between the two treatment groups (moclobemide or placebo). Similar FBL values were observed in both groups (group A *vs* B): during the first week the FBL values were (mean ± SD) 0.40 ± 0.23 ml/day *vs* 0.55 ± 0.53 ml/day on days 1-3 and 0.40 ± 0.21 ml/day *vs* 0.37 ± 0.13 ml/day on days 4-7. The increase in FBL during the second week was comparable in both groups, with and without moclobemide (days 8-10: 0.78 ± 0.59 ml/day *vs* 0.80 ± 0.58 ml/day; days 11-14: 1.49 ± 0.95 ml/day *vs* 1.28 ± 0.62 ml/day). A decline in FBL was observed during the third week under placebo in both groups, but baseline values were not reached during the observation period. Again there was no difference between the two groups (days 15-17: 0.91 ± 0.52 ml/day *vs* 0.92 ± 0.47 ml/day; days 18-21: 0.74 ± 0.30 ml/day *vs* 0.68 ± 0.48

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ml/day). No statistically significant interaction was found between week and type of treatment, indicating that no significant influence of moclobemide on the ibuprofen-induced faecal blood loss occurred. No notable pharmacokinetic interaction between moclobemide and ibuprofen was observed. Moclobemide plasma concentration-time profiles with and without concomitantly administered ibuprofen were superimposable. The results demonstrate that the concomitant administration of ibuprofen and moclobemide to healthy volunteers does not result in a clinically significant interaction, either at the pharmacodynamic (faecal blood loss) or at the pharmacokinetic level.

KEY WORDS

ibuprofen, moclobemide, gastrointestinal bleeding, pharmacokinetic interaction

INTRODUCTION

Moclobemide selectively inhibits monoamine oxidase type A and has been shown to be efficacious in the treatment of depression /1,2/. A pharmacological screen in laboratory animals showed that high doses (100 mg/kg) of moclobemide potentiated the antiphlogistic and antiinflammatory activity of ibuprofen (data on file, F. Hoffmann-La Roche Ltd., Basel). Non-steroidal antiinflammatory drugs (NSAIDs) are known to have adverse effects, notably in the gastrointestinal tract, by inducing gastrointestinal bleeding. Increasing attention is being focused upon inherent safety problems related to their gastroenteropathy. The present study was designed to investigate whether, at therapeutic doses, there is an interaction between moclobemide and ibuprofen-induced faecal blood loss (FBL) in man, and whether this interaction could affect the safety of the two drugs when given in combination.

Faecal blood loss, assessed by measurement of faecal radioactivity after radiolabelling erythrocytes with ^{51}chromium, was compared between two groups each of 12 healthy volunteers, who were administered either moclobemide (150 mg t.i.d.) or placebo together with ibuprofen (600 mg t.i.d.). At the same time, the study provided the opportunity to investigate the pharmacokinetic

aspects of concomitant administration of moclobemide and ibuprofen.

After oral administration, moclobemide and ibuprofen are rapidly absorbed with peak plasma concentrations attained between 0.5 and 1.5 hours. Moclobemide has a high hepatic extraction ratio (blood clearance: 30-40 l/h), which leads to a substantial first-pass effect and to a rapid elimination of the compound ($t_{½}$: 1-2 hours); its volume of distribution at steady state is about 80 l, suggesting an extensive distribution out of the blood stream. Only 50% of the drug is bound to plasma proteins and it is therefore unlikely to undergo drug-drug interactions involving drug displacement /3/. Ibuprofen has a short elimination half-life (2-2.5 hours) and is eliminated mainly by biotransformation. It is highly bound to plasma proteins (more than 99%) /4/.

MATERIALS AND METHODS

Twenty-four volunteers were included in this double-blind, placebo controlled trial. Pre- and post-treatment screenings included a medical history, a complete physical examination, haematology, serum chemistry and urinalysis evaluations. Excluded were subjects with a history or current evidence of cardiovascular, hepatic, renal, allergic, or significant gastrointestinal (peptic ulcer, haemorrhoids) disease, spontaneous nosebleeds or gingival disease; also excluded were subjects who smoked more than 10 cigarettes a day, who had used any prescription or over-the-counter drug in the 14 days before the study, and those who had participated in a study within 60 days prior to the start of the present trial.

The study protocol was subjected to institutional review board approval and written informed consent was obtained from each individual prior to inclusion in the trial, after adequately explaining aims, methods, objectives and potential hazards of the procedures. The study was conducted in accordance with the principles laid down in the declaration of Helsinki, as amended in Tokyo, Venice and Hong Kong, concerning biomedical research involving human subjects.

To allow monitoring of faecal blood loss, the volunteers' erythrocytes were labelled with ^{51}chromium three days before the start of moclobemide or placebo administration. In the human body this label is eliminated from the circulation with a half-life of around 20-30 days /5/. Labelling was achieved by drawing a 20-ml

blood sample from an antecubital vein into a sterile heparinized syringe; this blood was transferred into a sterile 50-ml flask containing 3 ml of acid citrate dextrose solution (British Pharmacopoeia) and 0.2-0.25 mCi of sodium ^{51}chromate solution (1 mCi/ml physiologic saline solution, Amersham, Whitchurch and Cardiff, UK). The contents were mixed by swirling the flask gently. After one hour's incubation at 37°C, erythrocyte tagging was halted by the addition of 100 mg sterile ascorbic acid. The erythrocyte suspension was then reinfused.

With respect to the first and the second treatment weeks (days 1-14), the 24 volunteers were randomly allocated to a group of 12 volunteers (group A: 12 males, age 19-40 years, weight 70-93 kg) who were to receive 150 mg moclobemide (t.i.d.) or to another group of 12 volunteers (group B: 12 males, age 21-30 years, weight 64-96 kg) who were to receive matching placebo tablets (t.i.d.) instead of moclobemide. During the second treatment week (days 8-14), all 24 volunteers additionally received 600 mg ibuprofen (t.i.d.). Moclobemide and ibuprofen were given at time intervals of 8 hours (8 am, 4 pm, 12 pm). Subsequently, there was a wash-out period during which all the subjects received placebo t.i.d. alone (days 15-21). During the entire study period, the volunteers fasted every night from 22.00 h until breakfast was provided in the morning. No breakfast was ingested on the days when a complete series of blood samples was collected (days 7, 8, 14). The volunteers remained at the Clinical Research Center from the evening before the first drug (moclobemide or placebo) administration until day 19.

Using Vacutainer® tubes containing EDTA, blood samples were collected for moclobemide (profiles on days 7 and 14 with sampling times at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8 hours after the morning administration) and ibuprofen (profiles on days 8 and 14 with the same sampling times as for moclobemide) determinations, including trough level determinations of both drugs in the morning of days 9, 11 and 13. Serum samples for ibuprofen protein binding determinations were additionally collected on day 8 (first ibuprofen dose) and 14 (last ibuprofen dose) before and 1 and 5 hours after the ibuprofen administration.

The determination of FBL was based on the measurement of ^{51}chromium in blood and stools. Blood was collected into EDTA Vacutainer® tubes every second day to determine the radioactivity decay curve in each subject. The volunteers collected their stools during the entire study period (days 1-21). Hospitalization of the

volunteers in the Clinical Research Center during the study period was an important measure to ascertain reliable and complete faeces collection. The counts in faeces corresponding to a certain volume of blood during a faeces collection interval were interpolated from the individual's ^{51}Cr concentration curve in blood. Faecal blood loss (FBL) was expressed as the volume of blood (ml) in the faeces during a collection interval. FBL was calculated by dividing the number of counts for total stool by the number of counts per ml of blood at the mid-point of the faeces collection interval. For all radioactivity counting procedures, a gamma-chromatograph equipped with a hyperpure germanium crystal was used (type: GEM-452005, EG and G, Ortec, USA). Containers with blood or faeces were introduced into the counter and counting was conducted automatically for 15 min. The standard deviation of counting was less than 9%.

Moclobemide was determined in plasma using a previously established HPLC method with UV detection /6/. The detection limit of the assay was 0.030 mg/l. The reproducibility and the accuracy of the method were determined from quality control samples which were analyzed during a pre-assay period and with every batch of study samples. Good reproducibility and accuracy of the method were observed with a coefficient of variation lower than 4% and a mean bias of -2 to +3%. The reproducibility of the assay, determined from repeatedly analyzed study samples, showed a mean coefficient of variation of 2.9% (n=520).

Ibuprofen was determined in plasma using an HPLC method with mefenamic acid as internal standard. After a deproteinization step for sample clean-up, separation of parent compound and internal standard from plasma constituents was achieved on a Nucleosil C-18 column using a mixture of acetonitrile and 0.05 M phosphoric acid (65:35, v/v) as the mobile phase (flow-rate: 1.2 ml/min). The eluent was monitored at λ=228 nm. The linearity of the method was investigated and found to be excellent over a range of 0.5 to 40 mg/l with correlation coefficients in the regression analysis ranging between 0.999 and 1.00. During the assays, quality control samples with concentrations of 1.00, 16.0 and 32.0 mg/l were analyzed in duplicate with each batch of samples. The results showed that the method had a good reproducibility (coefficient of variation less than 5%) and accuracy (bias ranging from -1.0 to +0.6%).

Ibuprofen and moclobemide plasma concentration-time curves were analyzed by model-independent methods. The maximum

plasma concentrations during the 8-hour profiles (C_{max}) and the time of their occurrence (t_{max}) were read from the observed data points. The beginning of the terminal log-linear phase was estimated by eye and its slope (β) was then calculated by log-linear regression analysis. The elimination half-life ($t_{½}$) was calculated from $\ln 2/\beta$. Areas under plasma concentration-time curves (AUC) were calculated up to the last sampling point (8 h) by the linear trapezoidal rule; the areas under plasma concentration-time curves after the administration of ibuprofen on day 8 were extrapolated to time infinity as described by Riegelman and Collier /7/. The total clearance (Cl/F) and the volume of distribution (V_β/F) were calculated as follows:

$$Cl/F = \frac{Dose}{AUC_0^8} \quad \text{and} \quad V_\beta/F = \frac{Cl/F}{\beta}$$

For the calculation of ibuprofen Cl/F on day 8, the extrapolated AUC (AUC_0^∞) was used. For the statistical evaluation, the parameters faecal blood loss (FBL), AUC_0^∞, AUC_0^8, C_{max}, $t_{½}$ and trough level values were log transformed.

Time profiles of changes in FBL were compared between the placebo group and the moclobemide group. A variable lag-time between bleeding and the detection of blood in stool occurs, depending on the transit time of faeces through the gastrointestinal tract. Because of this lag-time it was not possible to ascribe measured blood loss to an exact time point. Therefore, the statistical analysis of the changes in FBL during this study was performed after dividing each week of the study into two blocks of 3 and 4 days. Two separate analyses of variance were then performed, one using the FBL values averaged over the first 3 days and one using the FBL values averaged over the last 4 days of each week. The factors treatment (moclobemide or placebo), time (weeks 1, 2 and 3 of the study), volunteers and the interaction treatment x week were used (Proc GLM of SAS, Cary, NC). According to the split-unit design of the study the 24 subjects were the main units. Because ibuprofen was only administered in week 2, the interaction treatment x week describes the influence of moclobemide on the ibuprofen-induced faecal blood loss. To test for treatment effects, a between-volunteer analysis was performed. Pairwise comparisons between the weeks were based on least-square means. A significance level of $\alpha = 0.05$ was used.

For the mean trough levels and for the kinetic parameters of ibuprofen (AUC, C_{max} and t_{max}), analyses of variance were

performed with the factors treatment (moclobemide or placebo), time (days 8 and 14), volunteers nested in treatment group and with the interaction treatment x day. For comparison of the kinetic parameters of moclobemide (AUC_0^{τ}, C_{max}, $t_{½}$ and averaged trough levels) at different observation time points, analyses of variance were used with the factors time and volunteer.

The parameter t_{max} was rounded to the next quarter of an hour. To test for treatment (moclobemide or placebo) influences on the ibuprofen t_{max} data, 2-sample Wilcoxon tests were used for each day (8 and 14) (Proc NPAR1WAY of SAS, Cary, NC). To test for a change in t_{max} over time, the signed rank test was used for both (ibuprofen and moclobemide) drugs (Proc PAIRED of SAS, Cary, NC).

RESULTS

As expected, during the first week of the study (days 1-7), blood loss was below 1 ml/day in both groups of volunteers; it increased during the coadministration of ibuprofen in week 2 and the highest FBL values were attained on days 11 to 14 in the two groups of volunteers. During the wash-out phase, volunteers of both groups received placebo and their faecal blood loss decreased, although it was still significantly above baseline at the end of the third week (days 18-21) (Table 1). Values of faecal blood loss on individual days are depicted in Figure 1.

Statistical analysis of the changes in faecal blood loss during this study showed no significant interaction between week and treatment, indicating that FBL was not different in the placebo and moclobemide groups. Similar FBL values were observed in both groups (group A *vs* B) during the first week (days 1-3: 0.40 ± 0.23 ml/day *vs* 0.55 ± 0.53 ml/day; days 4 to 7: 0.40 ± 0.21 ml/day *vs* 0.37 ± 0.13 ml/day). The FBL increase was comparable in both groups, with and without moclobemide (days 8-10: 0.78 ± 0.59 ml/day *vs* 0.80 ± 0.58 ml/day; days 11-14: 1.49 ± 0.95 ml/day *vs* 1.28 ± 0.62 ml/day). In both groups, a decline in FBL was observed during the third week under placebo, but baseline values had not been reached at the end of the observation period. Again no statistical difference was obtained between the two groups (days 15-17: 0.91 ± 0.52 ml/min *vs* 0.92 ± 0.47 ml/day; days 18-21: 0.74 ± 0.30 ml/day *vs* 0.68 ± 0.48 ml/day). The statistical analysis of the last 4 days of each treatment week would have shown a significant moclo-

TABLE 1

Mean (± S.D.) values of faecal blood loss (ml/day) during the three weeks of the study in both groups of volunteers (averages of days 1 - 3 and 4 - 7 in each week)

Days of the study	Moclobemide group (group A)	Placebo group (group B)
Week 1:		
1 - 3	0.40 ± 0.23	0.55 ± 0.53
4 - 7	0.40 + 0.21	0.37 ± 0.13
Week 2:		
8 - 10	0.78 ± 0.59[a)]	0.80 ± 0.58[a)]
11 - 14	1.49 ± 0.95[b)]	1.28 ± 0.62[b)]
Week 3:		
15 - 17	0.91 ± 0.52[a)]	0.92 ± 0.47[a)]
18 - 21	0.74 ± 0.30[b) c)]	0.68 ± 0.48[b) c)]

[a)]statistically higher than days 1 - 3 (week 1)
[b)]statistically higher than days 4 - 7 (week 1)
[c)]statistically lower than days 11 - 14 (week 2)
[significance level $\alpha \simeq 0.05$]

bemide-ibuprofen interaction with a probability of 80% ($\alpha = 0.05$) had the true influence of moclobemide resulted in a 130% increase of the ibuprofen-induced faecal blood loss; hereby it is assumed that no increase in FBL due to moclobemide can be observed during the wash-out period.

Within the moclobemide and placebo treatment groups, a statistically significant change of FBL over time was observed, using the *first three days* of each week (days 1 to 3, 8 to 10, 15 to 17); pair-

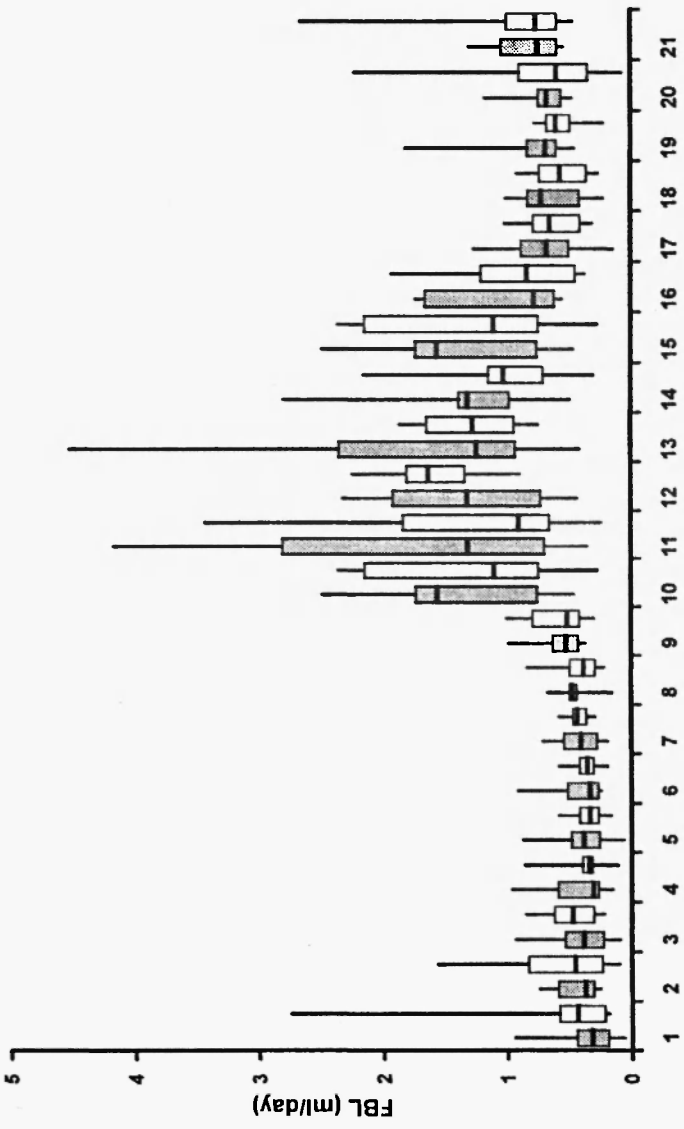

Fig. 1: Box-whisker plot of ibuprofen-induced faecal blood loss (ml/day) in moclobemide (hatched boxes) and placebo (plain boxes) groups. Boxes give interquartile range showing difference between the individual first and third quartiles, vertical bars indicate the range from lowest to highest observed value and horizontal bars the median.

wise comparisons showed a statistical difference between week 1 and week 2, between week 1 and week 3, but not between week 2 and week 3. Comparing FBL at the end of each week of the study (days 4 to 7, 11 to 14 and 18 to 21), FBL was significantly higher at the end of the second week compared to the first week; the blood loss declined after the cessation of ibuprofen coadministration (week 3) and was statistically significantly lower than during week 2, but remained statistically higher than during week 1 (Table 1).

Moclobemide plasma concentration-time profiles, measured on day 7 (before ibuprofen administration) and 14 (during concomitant ibuprofen administration) allowed a good estimation of pharmacokinetic parameters at steady state (Figure 2). Moclobemide steady-state concentrations were achieved on day 5 (C_{ss},min: 0.49 ± 0.23 mg/l); concentrations were relatively constant throughout the remainder of the study period. A statistical comparison made between moclobemide mean trough levels on days 5 and 7 (before ibuprofen coadministration) *vs* days 9 and 11 (during ibuprofen coadministration) revealed no difference. Moclobemide pharmacokinetic parameters are summarized in Table 2. No significant change occurred in t_{max} and C_{max} values of moclobemide between day 7 (t_{max}: 1.0 ± 0.7 h; C_{max}: 1.95 ± 0.37 mg/l) and day 14 (t_{max}: 1.2 ± 0.8 h; C_{max}: 1.86 ± 0.29 mg/l) (Table 2). Areas under the curve during a dosing interval (AUC_0^τ) remained unchanged during concomitant ibuprofen administration and no difference was observed in oral clearance (Cl/F) between day 7 (21.7 ± 11.9 l/h) and day 14 (21.1 ± 12.5 l/h). Moclobemide elimination half-life ranged from 1.45 to 3.74 hours before ibuprofen administration, and from 1.37 to 3.89 hours during ibuprofen coadministration. Statistical analysis showed that moclobemide elimination half-life decreased significantly from day 7 to day 14 (decrease: 0.15 ± 0.19 h).

Ibuprofen pharmacokinetic parameters on days 8 and 14, in both groups of volunteers, are summarized in Table 3. Statistical analyses of the main ibuprofen parameters (C_{max}, $t_{1/2}$, AUC) revealed no significant differences in the absorption and disposition of this NSAID in the absence and presence of steady-state concentrations of moclobemide. Mean elimination half-lives were 1.72 ± 0.21 hours on day 8 and 1.76 ± 0.30 hours on day 14 in the placebo group; in the group of volunteers who concomitantly received moclobemide they were 1.78 ± 0.18 hours on day 8 and 1.94 ± 0.52 hours on day 14. Peak concentrations were achieved rapidly (placebo group, t_{max}: 1.3 ± 0.7 and 1.1 ± 0.9 hours on day 8 and 14, respectively). Almost identical maximum concentrations

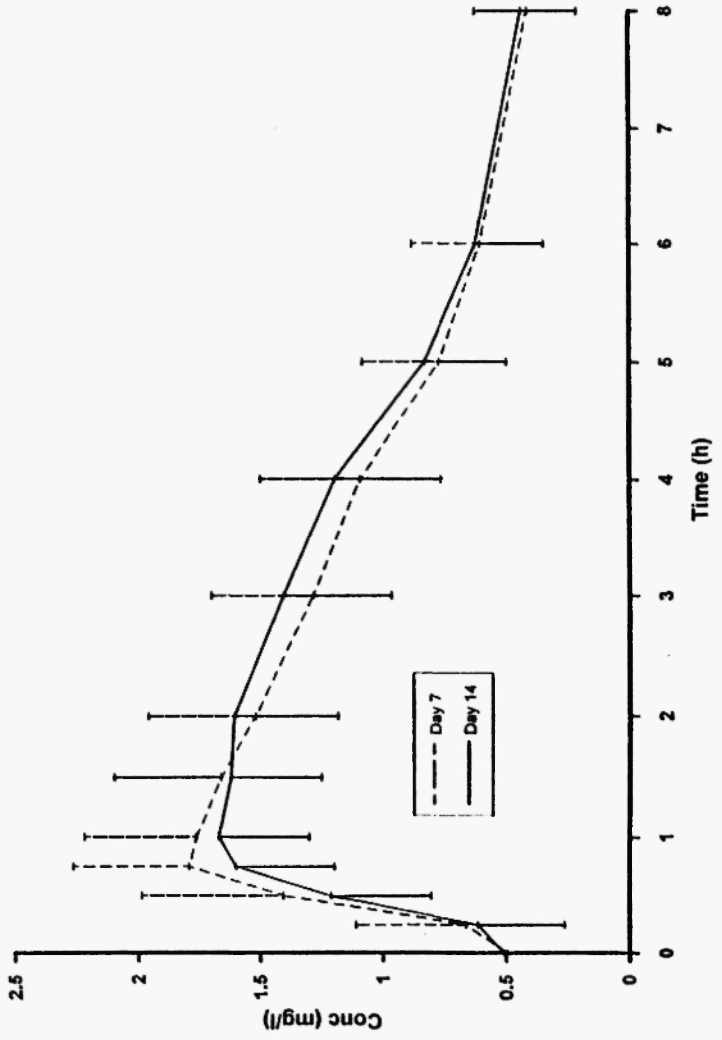

Fig. 2: Plasma concentration-time profiles (mean ± SD) of moclobemide before (day 7) and after (day 14) administration of ibuprofen 600 mg t.i.d.

TABLE 2

Mean (± S.D.) pharmacokinetic parameters of moclobemide on days 7 and 14 during a multiple oral dosing regimen of 150 mg moclobemide three times a day

Day	t_{max} (h)	C_{max} (mg/l)	Cl/F (l/h)	V/F (l)	$t_{1/2}$ (h)
Day 7[1]	1.0 ± 0.7	1.95 ± 0.37	21.7 ± 11.9	80.8 ± 17.6	2.69 ± 0.91
Day 14[2]	1.2 ± 0.8	1.86 ± 0.29	21.1 ± 12.5	74.3 ± 14.4	2.55 ± 0.86

[1] before concomitant ibuprofen administration
[2] after 1 week of concomitant ibuprofen administration

TABLE 3

Mean (± S.D.) pharmacokinetic parameters of ibuprofen on days 8 and 14 during an oral dosing regimen of 600 mg t.i.d. ibuprofen in subjects with moclobemide and placebo coadministrations

Day	t_{max} (h)	C_{max} (mg/l)	Cl/F (l/h)	V/F (l)	$t_{1/2}$ (h)
Day 8[1]					
Moclobemide group	1.5 ± 1.0	39.6 ± 6.9	4.1 ± 0.4	10.6 ± 1.4	1.78 ± 0.18
Placebo group	1.3 ± 0.7	43.6 ± 8.3	4.2 ± 0.5	10.3 ± 0.9	1.72 ± 0.21
Day 14					
Moclobemide group	1.8 ± 1.4	37.7 ± 9.6	3.9 ± 0.6	11.3 ± 4.9	1.94 ± 0.52
Placebo group	1.1 ± 0.9	42.0 ± 8.9	4.0 ± 0.6	9.9 ± 1.1	1.76 ± 0.30

[1] first administration of ibuprofen

were seen in both groups of volunteers with no change from day 8 to day 14 (C_{max}: day 8, 43.6 ± 8.3 mg/l *vs* 39.6 ± 6.9 mg/l; day 14, 42.0 ± 8.9 mg/l *vs* 37.7 ± 9.6 mg/l). In the moclobemide group a slight increase was observed in mean elimination half-life from day 8 to day 14; the difference did not reach statistical significance and was mainly due to the slow ibuprofen elimination in one subject where difficulties in the estimation of the elimination half-life were encountered. Ibuprofen serum protein-binding was determined in both groups on day 8 and on day 14 (predose, 1 and 5 hours following administration). Serum protein binding was the same in group A [mean fraction unbound fu at 1 and 5 h: 0.29 (day 8), 0.31 (day 14)] and group B [mean value of fu at predose, 1 and 5 h sampling time: 0.31 (day 8) and 0.31 (day 14)], confirming the absence of an influence of moclobemide coadministration.

DISCUSSION AND CONCLUSIONS

The influence of the concomitant administration of ibuprofen and moclobemide to healthy volunteers was assessed at two different levels: at a pharmacodynamic level, with the measurement of faecal blood loss induced by ibuprofen, and at a pharmacokinetic level, with an evaluation of the pharmacokinetic parameters of moclobemide and ibuprofen during the concomitant administration of both drugs.

As expected, ibuprofen administration induced an increase in FBL, but this increase was similar in both groups of volunteers. The statistical analysis revealed no difference between the two study groups in either of the study periods, indicating that moclobemide had no significant additional effect on bleeding induced by ibuprofen. An analysis of the power in the statistical comparisons revealed that a 130%, or higher, increase of the ibuprofen-induced faecal blood loss caused by moclobemide (corresponding to an additional 2.0 ml/day blood loss) would have been detected in this study with a probability of 80% ($\alpha = 0.05$).

The mean daily blood loss in the subjects during the run-in period (week 1) was 0.43 ± 0.08 ml/day, in good agreement with baseline data reported from other studies in healthy volunteers /8-10/. Furthermore, ibuprofen-induced bleeding in our study was comparable to that found by other investigators (1.2 - 2 ml/day) who examined this NSAID at the range of the highest recommended dose (2400 mg/day). The treatment period of one week

with ibuprofen is sufficient to reach steady state in faecal blood loss because ibuprofen has a short elimination half-life (≃2 h) and steady-state concentrations are achieved rapidly. It has previously been shown that during treatment with ibuprofen over 40 to 50 days, FBL reached maximum values within one week of treatment /8/. On the other hand, maximum FBL values with piroxicam, isoxicam and tenoxicam, i.e. with NSAIDs characterized by a long elimination half-life, are only achieved after 3 or 4 weeks' treatment, confirming that the time course of induced FBL is linked to the pharmacokinetic characteristics of the drug /11-13/.

This study allowed the investigation of a possible pharmacokinetic drug-drug interaction between moclobemide and ibuprofen when administered concomitantly. Pharmacokinetic findings for ibuprofen revealed no statistically significant differences between the two treatment groups in either the absorption parameters (C_{max}, t_{max}, AUC) or in the distribution/ elimination parameters (V_β/F, fu, $t_{½}$). Moclobemide plasma concentration-time profiles after 7 and 14 days of administration were essentially superimposable; no statistically significant change was observed in pharmacokinetic parameters when concomitantly administered with ibuprofen, with the exception of a slight decrease in moclobemide elimination half-life on day 14, compared to day 7. Absorption and disposition parameters of moclobemide in this study correlated well with those previously reported /3/.

In conclusion, this study showed that the concomitant administration of ibuprofen and moclobemide to healthy volunteers did not result in a significant interaction, either at the pharmacodynamic (faecal blood loss) or at the pharmacokinetic level.

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