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Flurbiprofen-aspirin interaction: a double-blind crossover study

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Summary

Fifteen patients with seropositive rheumatoid arthritis were treated for 2-week periods with 150 mg flurbiprofen daily and with flurbiprofen in the same dosage plus 3 g aspirin daily, the treatments being administered in random allocation. The results showed that there were no significant differences clinically between the two treatments. Serum levels of flurbiprofen were measured during both treatment periods in 4 patients. During the flurbiprofen and aspirin period there was a fall in the serum levels of flurbiprofen and both the rate of absorption of the drug and the amount absorbed were less. However, the apparent half-life of elimination of flurbiprofen was unchanged. No obvious reduction in clinical efficacy was apparent.

Key words: Flurbiprofen – aspirin – anti-inflammatory agents – arthritis, rheumatoid – pharmacokinetics

Introduction

Patients with rheumatoid disease are commonly treated with a number of different non-steroidal anti-inflammatory agents and as many of these drugs are administered concurrently it is important to establish any evidence of drug interaction and to assess serum levels while studying clinical efficacy.

Because aspirin is still looked upon as the drug of choice in the treatment of rheumatoid arthritis this drug was chosen to study any possible interaction with the new non-steroidal agent, flurbiprofen.

Method and materials

Fifteen patients with classical rheumatoid disease were chosen for the study. All satisfied the American Rheumatism Association criteria[8] and all were seropositive. The mean age of the patients was 48.2 years and the mean duration of disease 6.1 years. Prior to entry to the study all the patients had been receiving flurbiprofen regularly for at least 1 month.

The trial was conducted as a double-blind crossover comparative study, each treatment period lasting 2 weeks. Patients were given, in random allocation, either 150 mg flurbiprofen plus placebo daily (1 capsule of 50 mg flurbiprofen plus 2 placebo capsules 3-times daily) or 150 mg flurbiprofen plus 3 g aspirin daily (1

capsule of 50 mg flurbiprofen plus 2 capsules of 500 mg aspirin 3-times daily). The capsules were identical in all outward appearances.

Assessments were carried out by a single observer, who was unaware of the treatment order, on entry to the trial and on Day 14 of each period. The following assessments were included: (i) articular index, using the Ritchie *et al.*[7] method, (ii) grip strength,[4] (iii) ring size,[12] (iv) pain score,[5] (v) satisfaction score,[5] and (vi) patients' assessment of pain severity and duration of morning stiffness, using the Lee chart for recording.[4] On the day of each assessment the patients took their capsules exactly 4 hours before the time of their clinic appointment.

Serum profiles of flurbiprofen were carried out in 4 patients on Days 14 and 28 of the study. These patients attended the clinic having had no food from 10.00 p.m. the previous evening and only a cup of tea on waking. The first dose of flurbiprofen plus placebo or flurbiprofen plus aspirin was given and an indwelling catheter inserted into an arm vein. Blood samples were taken 0.75, 1.5, 3, 4, 5 and 6 hours after ingestion of the capsules. No other drugs were allowed that day. Flurbiprofen was measured as its methyl ester by gas chromatography using the internal standard technique.[3]

Results

Twelve of the 15 patients completed the study. The results of the assessments are summarized in Tables I and II. To determine the average daily pain scores, the mean was taken of the scores for Days 8 to 14 of each treatment period. As can be seen from Table I, when these were analyzed with Student's t-test there were no significant differences between the two treatments. Similarly, no difference was seen for efficacy.

Table I. Assessments of pain score and clinical efficacy

Assessment	Flurbiprofen plus placebo	Flurbiprofen plus aspirin	Standard error of difference
Pain score	3.0	2.9	0.2
Efficacy	3.0	2.9	0.3

Table II shows the results for duration of morning stiffness, articular index, grip strength and finger joint size. Again, no significant differences were found between the two treatment periods.

Table II. Assessment of objective parameters

Assessment	Flurbiprofen plus placebo	Flurbiprofen plus aspirin	Standard error of difference
Morning stiffness (hrs)	1.3	2.3	0.3
Articular index	18	16	1.6
Grip strength (mmHg):			
Right	62	67	3.8
Left	61	64	4.3
Joint size (mm):			
Right	286	285	2.5
Left	283	278	1.9

Serum levels

Serum levels of flurbiprofen were less when aspirin was taken concurrently, as is shown in Figure 1. This trend was observed in all 4 patients studied.

Figure 1. Mean serum concentrations of flurbiprofen after single oral doses of 50 mg flurbiprofen plus placebo or 50 mg flurbiprofen plus 1 g aspirin after a multi-dose regimen: 4 patients

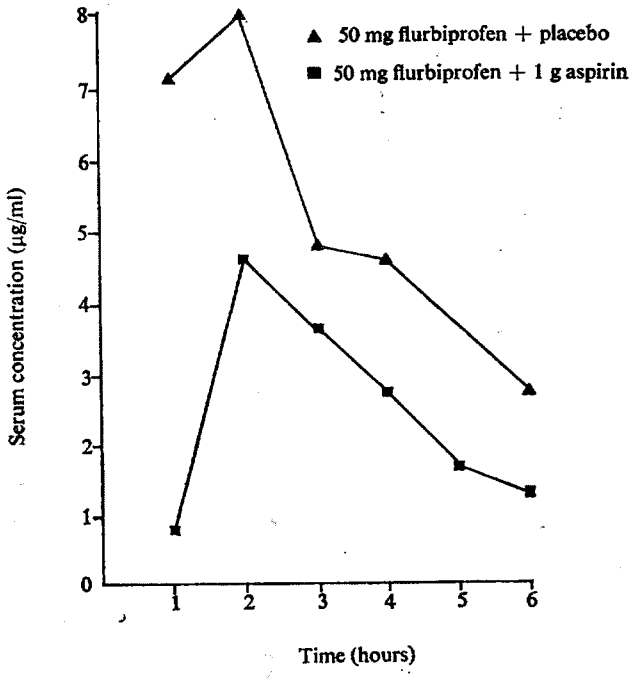

Table III. Areas* under serum concentration versus time curves (0 to 6 h) and apparent elimination half-life values for patients given 50 mg flurbiprofen plus placebo or 50 mg flurbiprofen plus 1 g aspirin after repeated dosage of the same combinations

Patient No.	Area (μg.h.ml^{-1})		Apparent elimination half-life (h)	
	Flurbiprofen plus placebo	Flurbiprofen plus aspirin	Flurbiprofen plus placebo	Flurbiprofen plus aspirin
5	36.3	19.1	2.9	2.4
7	42.3	14.4	2.3	1.9
9	23.3	11.8	2.1	2.9
13	20.7	18.3	3.1	2.6
Mean±S.E.M.	30.7±5.2	15.9±1.7	2.6±0.2	2.5±0.2

*calculated assuming no drug present at zero time

Integrated areas under the serum concentration against time curves were calculated by the trapezoidal rule using a programmed calculator. Apparent half-lives of elimination were determined, also using a programmed calculator, by least squares estimation, excluding the peak value. Details of the values for the apparent half-lives of elimination of flurbiprofen and the integrated areas under the serum concentration versus time curves are given in Table III. It can be seen from both Figure 1 and Table III that the rate of absorption of flurbiprofen and the amount absorbed, as reflected in the integrated areas, were both reduced when aspirin was taken concurrently, but the apparent half-life of elimination of the drug was unchanged.

Discussion

Both short-term[6] and long-term[11] studies of flurbiprofen have shown the drug to be effective in the treatment of rheumatoid disease and, in the long-term study, many of the patients were receiving other non-steroidal anti-inflammatory agents with no obvious evidence of interaction.

As aspirin is commonly used either as prescribed medication with other anti-inflammatory agents or as occasional self-medication, it is important to know if any interaction occurs between flurbiprofen and aspirin. Aspirin has been shown to decrease levels of other non-steroidal anti-inflammatory agents such as naproxen,[10] indomethacin, and fenoprofen.[9] Clinical studies have shown no significant interaction between a fixed dose of aspirin and indomethacin,[2] but Willkens and Segre[13] have shown an additive effect of naproxen in patients on individualized aspirin therapy. In this study using a fixed dosage of salicylate, no advantage of salicylate plus flurbiprofen together has been demonstrated.

The pharmacokinetic data suggest an interaction between aspirin and flurbiprofen with a reduction in the serum level of flurbiprofen. The exact mechanism for this interaction is still unclear, but it is interesting that both drugs are prostaglandin synthetase enzyme inhibitors.[1] Further work is at present underway in an attempt to elucidate this problem.

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