Clinico-pharmacological studies on ketoprofen ('Orudis')

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Summary

A study was made of the plasma and synovial fluid levels of ketoprofen after single oral doses of 50 mg. and 100 mg. given to patients with rheumatoid arthritis. The drug was rapidly absorbed and plasma levels were similar to those seen in healthy volunteers. The mean early plasma half-life of ketoprofen in both volunteers and patients with rheumatoid arthritis was 1.5 to 2 hours. An accumulative effect of ketoprofen was evident in the synovial fluid of the patients studied.

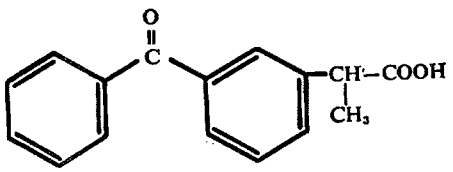
A double-blind crossover trial of ketoprofen (200 mg. daily) compared with placebo and aspirin (4.0 g. daily) was carried out in 24 patients with rheumatoid arthritis. Ketoprofen was shown to be significantly more effective than placebo in terms of pain relief, degree and duration of morning stiffness, articular index and patients' assessment of improvement. No significant differences were noted between ketoprofen and aspirin, although side-effects were less with ketoprofen.

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

Introduction

Ketoprofen ('Orudis'†), 2-(3-benzoylphenyl)propionic acid (Figure 1) is a compound with anti-inflammatory, analgesic and antibradykin activities demonstrable in animals.[9] It is chemically distinct but of the same therapeutic category as

Figure 1. Structural formula of ketoprofen



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ibuprofen and indomethacin. Previous studies have shown that ketoprofen in patients with rheumatoid arthritis is superior to placebo[3] and is well tolerated with a minimum of side-effects. It has also been shown to be at least as effective as salicylates, indomethacin and phenylbutazone in patients with osteoarthrosis.[1,8,15]

It is probable that the action of some anti-inflammatory drugs is related to their concentration in synovial fluid. Brooks *et al.*[2] have shown that the clinical parameters of inflammation fall to a minimum 1 to 2 hours after indomethacin plasma levels have reached a peak, which is approximately the time that indomethacin levels are maximal in synovial fluid.[7] It was considered desirable, therefore, to study the relation between the levels of ketoprofen in plasma and synovial fluid as well as the efficacy of the drug in patients with rheumatoid arthritis.

In this paper we report some initial observations on plasma and synovial fluid levels following a single oral dose of ketoprofen, and present the results of a double-blind crossover study of the efficacy of ketoprofen (given in a dose of 200 mg. per day) compared to placebo and aspirin (given in a dose of 4 g. per day) in a group of patients with rheumatoid arthritis.

Methods and materials

Plasma and synovial fluid levels

Encapsulated ketoprofen ('Orudis') was given to patients of both sexes who had been without food for at least 4 hours and all drug therapy for 24 hours prior to administration of this drug. Six patients were given 100 mg. ketoprofen and 5 patients were given 50 mg. ketoprofen. Blood was taken for analysis of ketoprofen level at regular intervals over the following 24-hour period. Three of the patients who took the 100 mg. dose and 2 of those who took the 50 mg. dose also had samples of synovial fluid taken regularly over the 6-hour period following ingestion of the drug. Blood and synovial fluid were collected in heparinised tubes, separated and the supernatent stored at –20°C until ketoprofen analysis was carried out.

Ketoprofen was measured by modification of the method of Populaire *et al.*[12] Essential differences involved the use of hexane – acetone (4:1, v/v) for the development of t.l.c. plates and the recovery of the methyl esters of ketoprofen and internal standard from the combined silica gel, after scraping from the t.l.c. plate, by extraction for 30 min. with toluene (1 ml.). An aliquot (10 μl.) of the toluene was injected on to a 6 ft. × 0.25 in o.d. g.l.c. glass column packed with 5% OV-17 on non-acid washed chromosorb W (80-100 mesh) and the compounds detected by a ^{63}Ni electron capture detector. The gas-liquid chromatograph was a Perkin Elmer F 11 and instrument parameters were: injection temperature setting 3; electron capture detector settings, temperature 4 and voltage 26; oven temperature 200°C; and carrier gas (oxygen-free nitrogen) flow 50 ml./min. The minimum sensitivity of the method was about 40 ng./ml. of plasma or synovial fluid.

Double-blind trial

All 24 patients taking part in the clinical trial had 'definite' or 'classical' rheumatoid

arthritis according to the criteria of the American Rheumatism Association.[14] Their mean age was 50.5±2.2 years, with a range of 38 to 69 years. There were 5 male and 19 female patients. Ten of the patients had subcutaneous nodules present and all 24 patients had Grade III X-ray changes.[9] The mean duration of arthritis was 9.8±2.0 years, with a range of 1.0 years to 28 years. The average functional capacity was 2.[16] A record was taken of past and current antirheumatic therapy. None of the patients previously had or was receiving corticosteroid therapy. Any known drug allergies were noted. Patients with a recent diagnosis of an active peptic ulcer, regional enteritis, ulcerative colitis, or evidence of bleeding from the gastro-intestinal tract, renal or hepatic disease, were excluded from the study, as were women of child bearing age. All patients agreed to participate in this study after a full explanation of its content and implications.

The design of the study was that of a double-blind crossover trial. All current therapy was discontinued 7 days before starting the trial, after which patients were randomly allocated aspirin, ketoprofen or placebo, with the crossover taking place after 7 days. The dosage of ketoprofen administered was 50 mg. by mouth 4-times a day, and aspirin 1 g. by mouth 4-times a day. The patient's subjective impression of pain was recorded as a scale of 0 to 4 (0 = no pain, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe). The degree of morning stiffness was assessed on a similar scale and the duration of morning stiffness was established in minutes.

The patient's own assessment of general progress was calculated from a scale 0 to 4 (where 4 = total remission, 3 = excellent, 2 = considerable, 1 = moderate, and 0 = slight remission). An assessment of the patient's progress was also made by the physician employing the same scale.

An articular index[13] of joint tenderness was performed and grip strength was estimated in each hand as the mean of 3 grip strength values using a rolled sphygmomanometer cuff with an initial reading at a basal level of 30 mm.Hg.[10] The circumference of the proximal interphalangeal joints of the fingers and the interphalangeal joints of the thumbs were measured on each hand using the plastic spring apparatus supplied by Geigy Limited.[17]

In addition, radioactive technetium studies were performed at the commencement of the study and also at each later assessment. A slight modification of the procedure described by Dick and his colleagues was used.[5] Approximately 200 μCi of ^{99m}Tc (as sodium pertechnetate) was standardised by counting for 2 minutes at 30 cm., using a thallium activated sodium iodide scintillation crystal and photomultiplier. The pulses were fed through a pulse height analyser (EKCO M5050) and digital rate meter (EKCO M5183A) and read from the latter. Thereafter, the dose was injected intravenously into an antecubital vein, great care being taken to ensure no extravasation of the dose at the time of injection. At 15 minutes after injection, counting was performed over both knees (always ensuring that each joint was measured in the same order on each occasion). Each count lasted 2 minutes. The scintillation counter was positioned 2.5 cm. above the joint being examined and counts over the joints were expressed as a percentage of the administered dose.

Statistical analysis of the results obtained in the clinical study was carried out using Student's t-test for paired samples.

Results

Plasma and synovial fluid levels

Ketoprofen is seen to be rapidly absorbed in patients with rheumatoid arthritis, peak plasma levels occurring within 2 hours of administration of oral doses of 50 mg. or 100 mg. ketoprofen, (Table I). Although there was some individual variation in drug plasma levels, ketoprofen tended to be well absorbed with mean peak plasma levels, occurring at 1 hour, of 5.54 μg./ml. (range 2.11 μg./ml. to 7.10 μg./ml.) with the 100 mg. dose of ketoprofen, and of 3.25 μg./ml. (range 1.91 μg./ml. to 5.18 μg./ml.) with the 50 mg. dose of ketoprofen. There is no correlation between the peak plasma level and the dose expressed in mg./kg.

Table I. Mean plasma levels (μg./ml.) of ketoprofen in patients with rheumatoid arthritis

Dose level of ketoprofen	Time (hours)									
	0	0.5	1	1.5	2	3	4	6	12	24
50 mg. (n=5)	0	2.86	3.25	2.48	1.94	1.08	0.66	0.44	0.08	0
100 mg. (n=6)	0	2.77	5.54	4.13	3.65	2.44	1.39	0.44	0.09	0

Figure 2. Plasma and synovial fluid levels of ketoprofen in 2 patients given a single oral dose (50 mg.) of ketoprofen

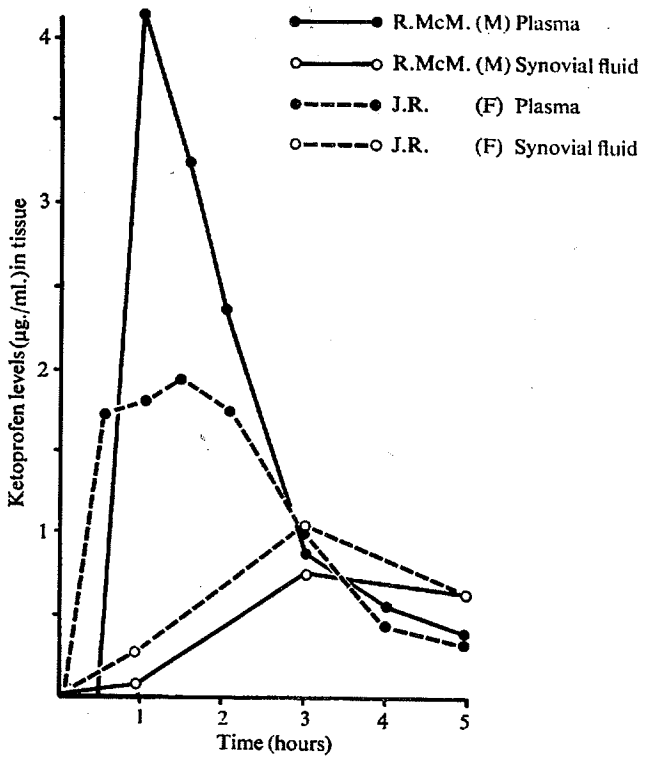
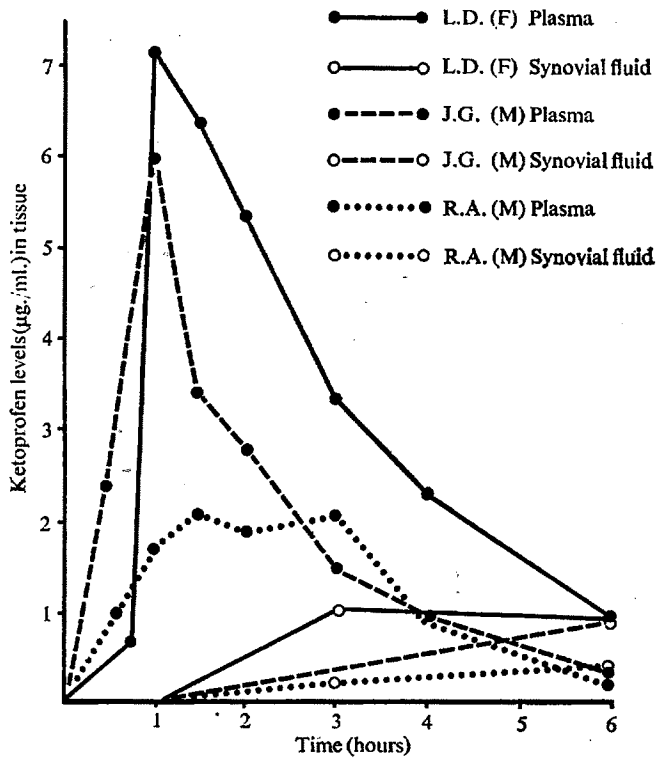


Figure 3. Plasma and synovial fluid levels of ketoprofen in 3 patients given a single oral dose (100 mg.) of ketoprofen



In those patients where blood and synovial fluid were sampled concurrently, the level of ketoprofen in synovial fluid reached a peak (mean level 0.91 μg./ml.) about 2 hours after the plasma maximum with the 50 mg. dose of ketoprofen, (Figure 2). The synovial fluid levels after the 100 mg. dose of ketoprofen (Figure 3) were almost stable during the 3 to 6 hours (mean level 0.70 μg./ml.) after administration of the drug.

Double-blind trial

In the clinical trial (Table II), it will be seen that there was a highly significant improvement in the pain scores, and in the patients' assessment of overall improvement with both aspirin and ketoprofen. The articular index, degree of morning stiffness together with duration of morning stiffness also showed significant improvement. Grip strength, joint circumference measurement and ^{99m}Tc uptake over both knees showed no significant change with treatment.

It is also interesting to note that 3 of the patients receiving aspirin suffered from marked nausea and 1 of these had troublesome vomiting. None of the patients receiving ketoprofen developed any apparent side-effects.

Table II. Clinical assessments in 24 patients after 50 mg. ketoprofen 4-times daily, and 1.0 g. aspirin 4-times daily: mean values ± S.E.M.

Assessment	Pre-trial	Placebo week	Aspirin week	Ketoprofen week	Placebo v. ketoprofen t	p
Pain level	1.66±0.15	3.25±0.20	1.95±0.18	1.95±0.16	6.23	0.001
Morning stiffness	1.75±0.12	3.29±0.17	2.0 ±0.18	2.04±0.18	6.25	0.001
Duration of morning stiffness (min.)	151±20	190±27	134±24	111±17	4.87	0.001
Articular index	18.2±2.4	26.0±2.7	21.0±2.6	20.29±2.6	4.4	0.001
Patients' assessment of progress		2.13±0.21	3.95±0.2	3.0±0.17	3.98	0.001
Joint circumference (mm.):						
Right	289±4.6	294±4	288±5	288±4	N.S.	
Left	290±4.6	287±4	290±5	290±4.5	N.S.	
Grip strength (mm.Hg.):						
Right	143±12	125±12	141±13	139±13	N.S.	
Left	146±12	131±11	141±14	145±14	N.S.	
Technetium uptake (%):						
Knee: Right		215±28	188±24	190±23	N.S.	
Left		192±27	192±28	189±28	N.S.	

N.S. = not significant

Discussion

Although some individual variation occurs, the early plasma kinetics of ketoprofen in patients with rheumatoid arthritis are very similar to those seen in healthy volunteers.[7] This suggests that the disease does not influence the pharmacokinetics of ketoprofen to any great extent. Ketoprofen is shown to penetrate the synovial fluid of arthritis patients and after 5 hours the approximate synovial fluild level exceeded the plasma level following a single oral administration. With the limited data available from this single-dose study, it was not possible to say if the apparent accumulation of ketoprofen in patients' synovial fluid was due to passive diffusion followed by binding of the drug to protein or other constituents of the arthritic joint, or by a facilitated transport mechanism. This point will be investigated further during a repeated oral dose study of ketoprofen in patients with rheumatoid arthritis.

The clinical study was designed to answer the question whether ketoprofen had analgesic and anti-inflammatory effects in patients with rheumatoid arthritis. The design of the study was simple, and the results show clearly significant improvement with ketoprofen compared with placebo in patients' assessment of their pain and overall well-being, the physician's assessment of the patient's progress, and in the articular index of joint tenderness. Morning stiffness showed improvement both in duration and severity with ketoprofen and the differences were significant. These results indicate that the drug has analgesic properties in rheumatoid arthritis. However, it is interesting to note that at no point was the improvement in any of the indices which occurred with ketoprofen statistically different from that which occurred with aspirin.

The problem of assessing an anti-inflammatory effect in patients with rheumatoid arthritis is bedevilled by the lack of sensitive indices.[4] No change was recorded in digital joint circumference, but it should be noted that the patients were selected on the basis of persistent pain in their joints, and not because they had soft-tissue

swelling in their finger joints. Much of the swelling in the small joints of the fingers in rheumatoid arthritis can be due to other than soft-tissue swelling and this, of course, will not be reduced by an anti-inflammatory drug. Consequently, because no change was observed in reduction of digital joint circumference, it cannot be concluded that aspirin and ketoprofen have no anti-inflammatory action. Similarly, it cannot be concluded that the drugs have no anti-inflammatory action because no statistical difference in joint 'uptake' of ^{99m}Tc could be demonstrated. In this context it is interesting to note that some anti-inflammatory effect has been demonstrated in animal pharmacological studies,[9] and similar activity has been suggested from the results of a single previous clinical trial.[11]

The conclusions of the clinical study are that by the oral route ketoprofen (200 mg. daily) has an analgesic effect equivalent to aspirin (4.0 g. daily) and superior to placebo in patients with rheumatoid arthritis and that no side-effects of ketoprofen therapy were observed.

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