Double-blind Cross-over Study of Ketoprofen and Ibuprofen in Management of Rheumatoid Arthritis

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Summary

A double-blind cross-over study of ketoprofen (Orudis) 150 mg daily and ibuprofen (Brufen) 1,200 mg daily was carried out in 35 outpatients with rheumatoid arthritis. Results suggest that analgesic and anti-inflammatory activity of ketoprofen is superior to that of ibuprofen. Significantly greater pain relief ($P < 0.05$) and reduction in joint circumference ($P < 0.01$) was obtained with ketoprofen than with ibuprofen. Side effects of the drugs were comparable and not serious.

Introduction

Ketoprofen (Orudis), 2-(3-benzoylphenyl) propionic acid, is a new non-steroidal analgesic and anti-inflammatory agent, with a structure that bears a superficial similarity to the anti-inflammatory agent ibuprofen (Brufen), in that it has a β -phenyl-propionic group.

It has been shown to have potent analgesic, anti-inflammatory, and antibradykinin activities in studies in laboratory animals (Julou *et al.*, 1971).

Recent clinical studies have shown that ketoprofen is well tolerated by patients and has a low incidence of adverse reactions (G. Gomez, personal communication, 1972; D. W. Zutshi and R. M. Mason, personal communication, 1972).

In double-blind cross-over studies ketoprofen has been found to have significant analgesic and anti-inflammatory activity compared with placebo (Cathcart *et al.*, 1973; Zutshi *et al.*, 1973), and to have comparable therapeutic efficacy with indomethacin when given in equal dosage (Gyory *et al.*, 1972) in patients with rheumatoid arthritis and osteoarthritis of the hip.

Ibuprofen has been claimed as a useful analgesic and anti-inflammatory agent; it is significantly less potent than indomethacin but has a lower incidence of side effects (Owen-Smith and Burry, 1972; Hart, 1972).

The present study was designed to compare the analgesic and anti-inflammatory activities and side effects of ketoprofen and ibuprofen in patients with rheumatoid arthritis.

Patients and Methods

Thirty-five outpatients who satisfied the American Rheumatism Association criteria for definite or classical rheumatoid arthritis (Ropes *et al.*, 1959) were admitted to the trial (table I). All had evidence of joint inflammation and involvement of at least two proximal interphalangeal joints of the hands. Informed consent was obtained from patients, and their general practitioners were notified before the start of the trial.

Patients excluded were those who had received corticosteroids or antimalarial or immunosuppressive drugs during the previous three months; patients with a history of gastrointestinal, renal, or hepatic disease; women of child-bearing age (except one aged 42 years who had had a hysterectomy); and children. Patients satisfactorily stabilized on gold therapy were not excluded from the trial.

A double-blind cross-over technique was used, patients receiving two weeks' treatment of each trial drug in turn with the sequence determined by random allocation. The drugs were supplied in capsules of identical appearance containing either 25 mg ketoprofen or 200 mg ibuprofen, and patients were instructed to take two capsules three times a day with meals. Patients were also supplied with a known number of paracetamol tablets, 500 mg, to be used only for the control of severe pain. All unused capsules and paracetamol tablets were returned for counting. All other anti-inflammatory and analgesic treatment was stopped at the time of the initial assessment.

Patients were assessed on the first day of the trial, at two weeks, and at four weeks, by the same independent observer, at the same time of day for each patient.

Laboratory investigations included a full blood count, erythrocyte sedimentation rate (E.S.R.), standard liver function tests, and measurement of plasma proteins.

Subjective assessments were based on answers to standard questions.

Severity of pain (nil, slight, moderate, severe, very severe) and current clinical state (very good, good, fair, poor, very poor) were scored on a five-point scale grading severity of symptoms from 0 to 4. Duration of morning stiffness was recorded for quarter-hour intervals up to four hours, based on a 0 to 15 scale.

Side effects were noted in response to the standard question, "Has the treatment upset you in any way during the past week? If yes, in what way?" At the final assessment patients were asked to state a preference for the first or second fortnight of the treatment.

Objective assessments were of (a) grip strength—taken as the maximum of three readings made with each hand, and measured with a grip dynamometer attached to a sphygmomanometer and inflated to 30 mm Hg; (b) joint circumference—at the initial assessment the two proximal interphalangeal joints showing most signs of inflammation were chosen. These were measured on each occasion, using the Geigy instrument, and the mean of two readings for each joint was taken; and (c) E.S.R., which was

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TABLE I—Details of 34* Patients who Completed Study

Trial Drug Sequence	No. of Patients			Age (Years)		Duration of Illness (Years)			Functional Dependency†					Serology			Erosions		
	M.	F.	Total	Range	Mean	<1	1-5	>5	4	3	2	1	0	+ve	-ve	?	+	-	?
Ibuprofen/ketoprofen ..	4	12	16	38-83	59	2	8	6	1	7	4	4	0	14	2	0	10	4	2
Ketoprofen/ibuprofen ..	8	10	18	23-84	59	0	8	10	0	6	6	6	0	15	0	3	10	1	7

* One additional patient aged 84 died from concurrent disease, making a total of 35 patients admitted to the study.

† Modified after Steinbrocker *et al.* (1949), grade II being subdivided into two categories of severity of disability.

TABLE II—Subjective Assessments in 34 Patients Completing Study

	No Change	Uncertain	Ketoprofen Favoured	Ibuprofen Favoured	P Value
Severity of pain ...	17	0	13	4	<0.05
Duration of morning stiffness ...	14	0	12	8	N.S.
Current clinical state ...	13	0	9	12	N.S.
Drug preference ...	13	1	10	10	N.S.

N.S. = Not significant.

FIG. 1—Effect of treatment on severity of pain.

FIG. 2—Effect of treatment on joint circumference.

TABLE III—Objective Assessment in 34 Patients Completing Study

	Ketoprofen	Ibuprofen	Difference	Standard Error (S.E.)	Difference/S.E.	P Value
Grip strength (mm Hg) ...	156.40	149.86	6.54	4.6	1.4	N.S.
Joint circumference (mm) ...	60.80	61.17	-0.37	0.12	3.0	<0.01
E.S.R. (mm/hr) ...	48.18	44.94	3.24	1.52	2.13	<0.05

If normal deviate (Difference/S.E.) > 2.6 then $P < 0.01$; if > 2.0 then $P < 0.05$.
N.S. = Not significant.

measured at each visit by the Westergren method by the same observer.

The difference between the number of paracetamol tablets taken with each drug (the rescue drug count) provided an indirect comparison of the analgesic activity of the two drugs.

Results

Thirty-four patients completed the trial (table I). One woman aged 84 years died from thyrotoxic atrial fibrillation leading to a cerebral embolus in the first week of treatment with ibuprofen.

Statistically significant values favouring ketoprofen were obtained for pain relief ($P = < 0.05$), and reduction of joint circumference ($P = < 0.01$), reflecting analgesic and anti-inflammatory activity respectively (tables II and III). A cross-over effect of ketoprofen and ibuprofen for these two factors is clearly shown in figs. 1 and 2. There was, additionally, a trend in favour of ketoprofen in respect of morning stiffness, and grip strength, and in the rescue drug index (table IV).

There was a trend in favour of ibuprofen in assessment of current clinical state (not significant), and in reduction of E.S.R. ($P < 0.05$).

Adverse reactions (table V) occurred with equal frequency with both drugs. Symptoms of dyspepsia were more frequent with ketoprofen than with ibuprofen. However, none of the symptoms was severe with either drug and in no case necessitated withdrawal of trial medication.

TABLE IV—Difference in Number of Paracetamol Tablets Required between Treatment with Ketoprofen and with Ibuprofen

	No Change	Uncertain	Ketoprofen Favoured	Ibuprofen Favoured	P Value
No. of patients ...	4	3	16	11	N.S.

N.S. = Not significant.

TABLE V—Analysis of Symptoms in 34 Patients Completing Study

Symptoms	Ketoprofen (15 patients)	Ibuprofen (14 patients)
Gastrointestinal:		
Nausea	1	2
Heartburn	1	1
Abdominal pain	5	—
"Puffy" feeling in abdomen	1	—
Regurgitation	1	—
Vomiting	1	1
Diarrhoea	2	1
Constipation	—	1
Central nervous system:		
Depression	2	2
Lethargy	2	—
Headache	1	4
Giddiness	—	1
Others:		
Palpitations	1	—
Weight gain	1	—
Sore gums	1	—
Rash	—	3
Haemoptysis	—	1
Epistaxis	—	1
Frequency	—	1
Total	20	19

No. of patients without symptoms during treatment with ketoprofen, 6; ibuprofen, 7; both drugs, 13. No. with symptoms during treatment with both drugs, 8.

No patients were withdrawn or dropped out from the study. One patient aged 84 died from concurrent disease (thyrotoxicosis, atrial fibrillation, cerebrovascular accident) during treatment with ibuprofen.

Discussion

The present study was designed to compare ketoprofen 150 mg daily with ibuprofen 1,200 mg daily in the treatment of rheumatoid arthritis.

Cromie (1963) pointed out that gross alterations in formulations of trial drugs could possibly alter bioavailability, and theoretically the change in presentation of ibuprofen in the present study might have affected its bioavailability and reduced its effectiveness. However, the manufacturers (Boots) thought that the 200 mg capsules of ibuprofen used in this study were suitable for clinical trial purposes.

The results suggest that ketoprofen has analgesic and anti-inflammatory activity superior to ibuprofen. It is noted particularly that statistically significant differences in activity, favouring ketoprofen, were obtained even with the comparatively small number of patients used in this study. These results are consistent with those of Owen-Smith and Burry (1972) and Gyory *et al.* (1972), who showed, respectively, indomethacin 75 mg to have greater activity than ibuprofen 1,200 mg, and ketoprofen 100 mg to have comparable activity with indomethacin 100 mg.

Cardoe (1969) and Goldberg *et al.* (1971) reported an overall reduction in E.S.R. in patients with rheumatoid arthritis treated with ibuprofen. The reduction in E.S.R. in the present study favoured ibuprofen ($P < 0.05$), despite the reverse finding for joint circumference.

A factor influencing the therapeutic efficacy of drugs, both in clinical trials and in other clinical situations, is drug interaction. Ketoprofen has been shown to have no effect on hepatic drug-metabolizing enzymes, based on a study of plasma-clearance of antipyrine (Cathcart *et al.*, 1973), and is unlikely therefore to interact with drugs metabolized by the liver.

An important consideration in assessing the value of a new drug for treatment of rheumatoid arthritis is incidence of adverse reactions. A drawback to the use of indomethacin, a powerful analgesic and anti-inflammatory agent, is a relatively high

incidence of side effects. Ibuprofen has been found to be better tolerated, but its therapeutic efficacy has been questioned (Hart, 1972; Owen-Smith and Burry, 1972). Previous long-term studies of ketoprofen 150 mg daily have shown that this dose is well tolerated by patients, and is not associated with serious adverse reactions or with significant changes in biological values monitored at monthly intervals for up to 12 months (G. Gomez, personal communication, 1973). These findings are consistent with the present results in which side effects of ketoprofen and ibuprofen were found to be comparable and not serious.

In conclusion, the present study has shown that analgesic and anti-inflammatory activity of ketoprofen is significantly superior to that of ibuprofen, while adverse reactions of the two drugs are comparable and not serious. This is further evidence that ketoprofen may be a useful drug in the clinical management of rheumatoid arthritis.

Requests for reprints should be sent to Dr. F. E. Bruckner.

Ketoprofen will be available in the United Kingdom from next month.

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Tetracycline-resistant Beta-haemolytic Streptococci in South-west Essex : Decline and Fall

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Summary

The prevalence of tetracycline-resistant beta-haemolytic streptococci in South-west Essex has been recorded over the past 10 years. It has fallen from a peak of 35% in 1965 to a level of 9.2% in 1972. Ear infections no longer provide the highest incidence of these organisms; vaginal, perineal, and skin infections now seem to be of greater relative importance but throat swabs still provide the greatest actual number of isolations. Erythromycin-resistant strains are still rare.

Introduction

Tetracycline-resistant beta-haemolytic streptococci have often been recorded since 1960 and their incidence in South-west Essex has been monitored since 1963 (Robertson, 1965, 1968). The incidence rose to a peak of 35% in 1965, remained at 33.5% in 1966, and fell slightly to 27% in 1967, when it was speculated that the figures might have begun to decline.

Recent reports indicate that the incidence of tetracycline-resistant beta-haemolytic streptococci is indeed falling. A survey of these organisms causing ear, nose, and throat infections in London shows their incidence declining from 42% in 1967 to 27% in early 1971 (Rees, 1971). A level of 6% is recorded in Sweden (Kahlmeter and Kamme, 1972), though no previous figures for Scandinavia were found by these authors.

We present the figures for South-West Essex from 1968 to 1972. The methods of isolation and sensitivity testing were as previously used—that is, organisms were grown on blood agar base No. 2 (Oxoid) or sensitivity test agar (Oxoid) both containing 7% added horse blood. Antibiotic discs containing 10 µg of tetracycline, 10 µg of erythromycin, and 1.5 units of penicillin were applied, and the organism was regarded as resistant if it grew right to the edge of the disc on overnight incubation.

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