Sulindac

Trials of a new anti-inflammatory drug

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SUMMARY   Trials in patients with rheumatoid arthritis and osteoarthritis showed sulindac to be an analgesic with anti-inflammatory properties and at least as effective as aspirin. It was effective within 24 hours in doses of 300–400 mg daily. It had the advantages of twice daily administration and a lower incidence of gastric side effects than aspirin. Constipation, usually mild, occurred in 20–30% of cases. Like other anti-inflammatory drugs, it was effective in only a proportion of the patients.

There is no shortage of nonsteroidal anti-inflammatory drugs. A new compound should therefore have some advantage to justify its introduction. Sulindac is related to indomethacin and would have such an advantage if it combined the anti-inflammatory activity of indomethacin with a more acceptable incidence of side effects.

Sulindac is an indene analogue of indomethacin with similar anti-inflammatory potency in animal models but less tendency to cause gastric bleeding and ulceration (Van Arman *et al.*, 1972). It is well absorbed after oral administration with a plasma half-life of about 8 hours, it is excreted mainly in the urine as unchanged drug and sulphone metabolite. Another metabolite, the sulphide, can be detected in plasma and has a long half-life of about 18 hours. It is more active than sulindac in animal models of inflammation and may account for a major part of the anti-inflammatory effect (Hucker *et al.*, 1973).

Methods

Three double-blind trials were carried out, a short-term three-way crossover trial in rheumatoid arthritis (RA) and long-term studies in both RA and osteoarthritis (OA).

CROSSOVER STUDY
Twenth-four outpatients with RA entered a crossover study, each receiving one week of treatment with aspirin (3·6 g daily in 4 divided doses), sulindac

(400 mg daily in 2 divided doses), and placebo. The order of treatment was randomised and balanced. Measurements made at the end of each week of treatment by a single observer included pain (visual analogue scale), duration of morning stiffness, proximal interphalangeal joint circumference (Boardman and Hart, 1967), articular index (Ritchie *et al.*, 1968), and drug preference. The patients completed a daily visual analogue pain relief scale which was used to determine the time course of the actions of the drugs.

LONG-TERM STUDY IN OA
Thirty outpatients with OA of the hip or knee were allocated randomly to two treatment groups. 14 patients received sulindac in an initial dose of 100 mg twice daily with the possibility of increasing up to a total daily dose of 400 mg. 16 patients received aspirin in an initial dose of 500 mg four times daily with the possibility of increasing up to a total daily dose of 4 g. Measurements were made by a single observer before the start of treatment and after 1, 2, 3, 4, 6, and 8 weeks of treatment. They included pain severity (visual analogue scale), duration of stiffness after inactivity, and side effects. The dose of trial drugs was noted at each visit and checked by returned tablet counting. Side effects were recorded, scored as either mild (1), moderate (2), or severe (3), and used to calculate side effect scores. The side effect score represented the sum of all side effects at all assessment visits. Urinalysis and full haematological and biochemical monitoring were performed. An electrocardiogram and an ophthalmological assessment were carried out at the beginning and end of the study.

LONG-TERM STUDY IN RA
Twenty-five patients with RA, including 21 who took part in the crossover study, were allocated randomly to two treatment groups. 13 patients received sulindac in an initial dose of 200 mg twice daily and 12 received aspirin in an initial dose of 1·2 g four times daily. The dose of both drugs could be reduced. After either 4 or 6 weeks' treatment, a 2-week placebo period was introduced and the patient then returned to his previous trial drug. Measurements made by a single observer before the start of treatment and after 2, 4, 6, 8, and 10 weeks were those used in the crossover study. Side effect collection and monitoring for toxicity were carried out as in the long-term study in OA.

The double placebo method was used to maintain blindness in all three studies, additional paracetamol was allowed, and the use of all drugs was checked by returned tablet counting. No other anti-inflammatory drug was allowed in any of the studies.

STATISTICAL METHODS
Differences within treatment groups and between treatment periods in the crossover trial were analysed by Student's t test applied to paired data. Differences between treatment groups were analysed by the unpaired t test. The χ^2 test was used to analyse numbers of patients with side effects, withdrawals, and preferences. The Mann Whitney U test was used to test changes in the duration of morning stiffness.

Results

CROSSOVER STUDY
Twenty-one patients completed the crossover study and the results are summarised in Table 1. Both aspirin and sulindac were superior to placebo in reducing pain and morning stiffness. Only sulindac produced a statistically significant reduction in proximal interphalangeal joint circumference, and other measurements showed a trend in favour of

sulindac though the differences between sulindac and aspirin were not statistically significant. There was a statistically significant preference for sulindac over placebo. The time courses of the actions of the drugs are shown in the Fig. Almost all the effects of sulindac were achieved within 24 hours of the start of treatment.

Examination of the responses to the two drugs compared with placebo showed a marked variation. Some patients responded to aspirin, and some failed to respond. Some patients responded to sulindac and some failed to respond. There was no significant correlation between response to aspirin and response to sulindac ($r=0·12$, $P>0·1$).

LONG-TERM STUDY IN OA
Both aspirin and sulindac produced a statistically significant reduction in pain and in the duration of inactivity stiffness. The significant reductions were achieved within the first week of treatment and changes thereafter were not statistically significant. There was no significant difference between the two drugs at any time. Some patients required an increase in dosage of both aspirin and sulindac. Doses required are shown in Table 2.
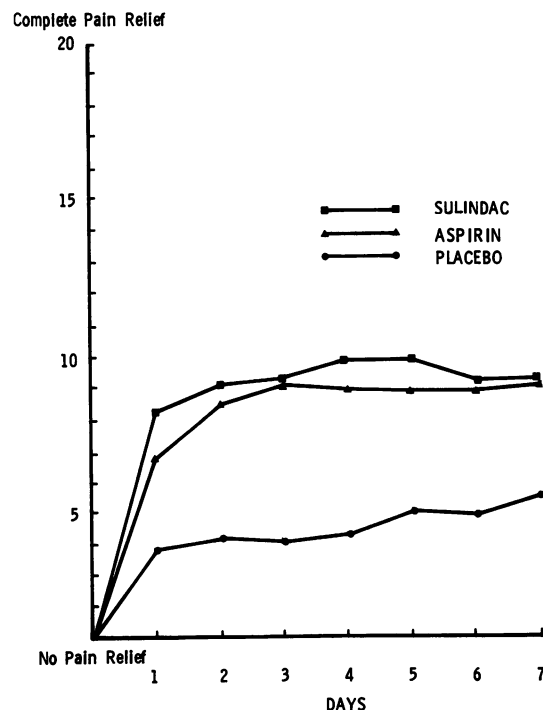

Fig.   Mean daily pain relief scores in patients receiving sulindac, aspirin, or placebo.

Table 1   Means of clinical measurements made at the end of one week's treatment with sulindac, aspirin, or placebo in a crossover study in 21 patients with rheumatoid arthritis.

	Sulindac	Aspirin	Placebo
Pain	10·3†	11·9†	14·6
Duration of morning stiffness (min)	75·7†	98·8*	189·5
PIP joint circumference (mm)	586·4*	589·5	590·7
Articular index	10·3	11·9	14·6

*Statistically significant difference compared with placebo (P <0·05)
†Highly significant (P <0·01)

Table 2 *Numbers of patients taking different dose levels of sulindac and aspirin for rheumatoid arthritis (RA) and osteoarthritis (OA). Aspirin dosage: 2, 3, or 4 g daily in OA; 3·6 or 4·8 g in RA*

Daily dose	No. of patients	
	OA	RA
Sulindac (mg)		
400	4	7
300	7	4
200	3	—
Mean daily dose	307	364
Aspirin (g)		
4 or 4·8	2	5
3 or 3·6	2	3
2	6	—
Mean daily dose	2·6	4·4

Table 3 *Side effect scores in patients with osteoarthritis receiving aspirin or sulindac. The first group are those which appeared to be commoner on aspirin, the second, commoner on sulindac. Headache was included to show that it didn't happen*

	Aspirin	Sulindac
Indigestion	16	7
Abdominal pain	6	2
Nausea/vomiting	5	0
Heartburn	3	0
Feeling unwell	6	0
Deafness/tinnitus	6	0
Constipation	4	16
Tiredness	4	13
Dry mouth	1	14
Headache	1	1
Others	43	36
Total	95	89

No patient was withdrawn from the sulindac group during the 10 weeks of the study. 6 patients (43%) were withdrawn from the aspirin group and this difference was statistically significant ($\chi^2=6·56$, P<0·02). Reasons for withdrawal were gastrointestinal disturbances in 3 patients, tinnitus and deafness in 1, lack of effect in 1, and gastrointestinal disturbance combined with lack of effect in 1.

The total incidence of side effects showed little difference between the two groups. Side effect scores are shown in Table 3. However gastric side effects were more common in patients receiving aspirin than in those receiving sulindac. Indigestion, abdominal pain, nausea, vomiting, or heartburn occurred in 10 patients on aspirin (63%) and 4 on sulindac (29%; $\chi^2=3·45$, 0·1>P>0·05). The three commonest side effects in patients receiving sulindac were constipation, tiredness, and dry mouth. Constipation occurred in 5 patients on sulindac (36%), but was mild in 4.

There were occasional minor abnormalities of biochemical measurements in both groups but no serious or clinically significant abnormalities were noted. There were no significant changes in the electrocardiogram or ophthalmological assessments.

LONG-TERM STUDY IN RA

The results of the long-term study in RA confirmed the results of the other two studies. Changes produced by the two drugs were similar and there was no significant difference between them except in changes in articular index after 2 weeks' treatment when patients on sulindac showed a significantly greater reduction (t=2·12, P<0·05). A reduction in proximal interphalangeal joint circumference was again seen in patients receiving sulindac (t=2·84, P<0·02).

Doses of both sulindac and aspirin required were slightly higher in RA than in OA patients (Table 2). 4 patients were withdrawn from the aspirin group and 2 from the sulindac group. Patients were withdrawn from the sulindac group because of lack of effect in one case and diarrhoea in another. Reasons for withdrawal of aspirin included lack of effect and gastrointestinal disturbances. Side effects were slightly less common on sulindac than on aspirin, gastric side effects were much less common, and constipation was more common.

During the 2-week placebo period, a relapse occurred as expected. Comparison of the treatment and placebo periods showed statistically significant differences in favour of sulindac in pain, morning stiffness, and articular index. Differences between aspirin and placebo were not statistically significant partly because withdrawals from treatment had made the size of the sample too small.

One patient with RA showed a raised alkaline phosphatase level (up to 300 IU) during treatment with sulindac. When the drug was withdrawn the level fell to normal. However, this biochemical abnormality was not associated with any clinical effects or changes in any other measurement and was considered irrelevant. No other adverse haematological or biochemical change was noted.

Discussion

These results suggest that sulindac is an analgesic anti-inflammatory drug of comparable potency to aspirin. In comparison with other major anti-inflammatory drugs like high dose aspirin or indomethacin, sulindac has two advantages. First it can be given twice daily. Previous studies have shown that twice daily is as effective as four times daily administration (Liebling *et al.*, 1975). Second, sulindac is well tolerated, seldom being withdrawn

because of side effects and with less tendency to cause gastric side effects than aspirin.

A low incidence of gastric side effects due to anti-inflammatory drugs is sometimes offset by reduction in effectiveness. This does not appear to be so with sulindac. It was at least as effective as aspirin and reduced joint size, the hallmark of traditional anti-inflammatory drugs (Boardman and Hart, 1967). Dieppe *et al.* (1976) found sulindac more effective than ibuprofen in OA and Calabro *et al.* (1974) found it effective in acute gout. Sulindac appears, like indomethacin, to be a major anti-inflammatory drug. It is therefore surprising that sulindac was less effective than indomethacin in ankylosing spondylitis (Gribnau and Lissone, 1975). Such apparent inconsistencies are already known in rheumatic diseases. Aspirin, for example, is as effective as phenylbutazone and indomethacin in RA but less effective in ankylosing spondylitis (Godfrey *et al.*, 1972). These differences may reflect different patterns of inflammatory mediators in different conditions. Sulindac is likely to be a useful alternative to indomethacin in RA and OA and the use of a new anti-inflammatory may please the group of patients who fail to do well on currently available compounds.

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