Indomethacin and Naproxen suppositories in the treatment of rheumatoid arthritis

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SUMMARY A double-blind cross-over study of 35 out-patients with rheumatoid arthritis showed that Naproxen and Indomethacin suppositories were both effective forms of treatment in rheumatoid arthritis, both being significantly superior to placebo in terms of relief of morning stiffness.

Indomethacin is a drug used widely in rheumatological practice. The oral dose employed is variable, but previous studies have suggested that one 100 mg suppository is as effective as 100 mg of capsules in relief of early morning stiffness in the treatment of rheumatoid arthritis.

More recently Naproxen tablets have been introduced as an analgesic, anti-inflammatory compound in the treatment of rheumatoid arthritis. At a dose of 500 mg it has been suggested that, of the available propionic acid derivatives, it is a drug of choice judged by patient preference. It produced the least number of unwanted effects compared with other drugs of this group (Huskinson *et al.*, 1976).

The results of a comparative trial between Indomethacin, Naproxen, and placebo suppositories are reported.

Material and methods

TRIAL DESIGN

Out-patients with rheumatoid arthritis were admitted to the trial at both King's College Hospital, London and Wrightington Hospital, Lancashire. The trial was three-way, double-blind, and of cross-over design. The suppositories contained Naproxen 500 mg or Indomethacin 100 mg or inactive placebo. The trial period was 3 weeks on each treatment. The suppositories were all the same colour and the placebo suppositories matched the Indomethacin suppositories; the Naproxen suppositories whilst they were of the same colour and design were slightly larger. Treatment was allocated randomly using all 6 possible orders of administration. During the trial, patients were allowed up to 3 g per day of Paracetamol as an escape drug. All other non-steroidal anti-inflammatory drugs were stopped 1

week before the start of the trial. Patients on stabilised dosage of penicillamine, gold, or corticosteroids were included in the study.

The efficacy of treatment was assessed initially and then at the end of each trial period by means of (1) Pain using the 10 cm visual analogue scale, range 'no pain' to 'worst ever pain' (Berry and Huskinson, 1972). (2) Early morning stiffness recorded in minutes. (3) Articular index using the method of Ritchie *et al.* (1968). (4) Ring size of the proximal interphalangeal joints. (5) Patient preference for the 3 treatments. (6) Doctor preference for the 3 treatments. (7) Blood levels were also measured in order to ascertain the absorption of Naproxen.

UNWANTED EFFECTS

These were elicited in 3 different groups. Proctoscopy: the results of this were recorded as normal, ulceration, erosion, oedema, erythema, or bleeding. Rectal symptoms were elicited by asking whether the patient had had any rectal problems. Different side effects were elicited by means of simple indirect question, 'Has the treatment upset you in any way?'.

Results

A total of 35 patients were admitted to the study, 11 male and, 24 female. All had erosive rheumatoid arthritis and 29 of the patients were sero-positive, 13 patients received no other therapy, 11 were taking penicillamine, 9 gold salts and 4 corticosteroids.

CLINICAL RESULTS

Pain measured on a 10 cm visual analogue scale was reduced by all 3 treatments. For Naproxen and Indomethacin the change was statistically significant at the $P < 0.05$ level. Both active

suppositories were superior to placebo. This reached significance in favour of Indomethacin ($P < 0.05$) but not Naproxen. There was no statistical difference between the active drugs.

Morning stiffness was significantly reduced by Naproxen ($P < 0.03$) and by Indomethacin ($P < 0.01$) but not by placebo. Both Naproxen and Indomethacin were significantly better than placebo in reducing morning stiffness ($P < 0.05$).

Improvement in articular index was seen with both drugs but not with placebo. However, only the change on Indomethacin was significantly superior to placebo ($P < 0.02$).

The difference between the active preparations was not significant. Ring size was reduced by all 3 treatments with no difference between their effects. (Table 1).

BLOOD LEVELS

Blood was taken from 29 patients for assessment of Naproxen levels. One patient showed no demonstrable Naproxen in his blood (he showed preference for placebo at the end of the trial!). The range of levels was from 5.2 to 78.6 $\mu\text{g/ml}$ of Naproxen. The mean was 32.7 $\mu\text{g/ml}$.

BOWEL HABIT

No change occurred during the study either in the frequency of bowel action or stool formation on any treatment.

Table 1 Clinical change (statistics based on Student's *t* test)

Pain		Morning stiffness (min)	Articular index	Ring size	
				Left	Right
Base	5.7	170	14.3	558	572
Changes					
I	-1.7	-77	-2.2	9	8
N	-1.4	-53	-1.6	9	8
P	-0.6	-12	+0.1	9	8
Statistics					
N&I	NS	NS	NS	NS	NS
N&P	$P < 0.08$	$P < 0.05$	NS	NS	NS
I&P	$P < 0.05$	$P < 0.05$	$P < 0.05$	NS	NS

I=Indomethacin. N=Naproxen. P=placebo

Table 2 Rectal side effects

	I	P	N
Rectal discomfort	7	6	2
Rectal bleeding	3	1	1
Soreness	0	1	2
Tenesmus	1	0	1
Flatus	2	0	1
Total	13	8	7

SIDE EFFECTS

Rectal

Less rectal side effects were reported from Naproxen than any other treatment, but this did not reach significance (Table 2). The results from proctoscopy are listed in Table 3. No ulceration or erosion occurred during the trial. However, oedema and erythema occurred frequently on the test drugs. Table 4 lists the general side effects. Rashes and gastro-intestinal side effects occurred with greater frequency on placebo, than with either active drug. There was marked discrepancy between the two centres in terms of the number of side effects reported (many more at Wrightington than at King's), but the actual number of patients developing side effects was similar.

WITHDRAWALS

Four patients discontinued therapy during the course of the study. Three had pain during the placebo period and the third had an unrelated admission to hospital.

PATIENT AND OBSERVER PREFERENCE

The physicians favoured Indomethacin (14 times), Naproxen (12 times), and placebo (5 times). The patients' preference was for Indomethacin (12), Naproxen (11), placebo (6), and no difference twice. There was no significant difference between these results.

Table 3 Incidence of side effects observed on proctoscopy

	I	P	N
Oedema	2	3	3
Erythema	7	4	8
Erythema and bleeding	1	1	1

Table 4 General side effects

	I	P	N
Nausea	4	5	1
Vomiting	2	2	0
Indigestion	3	5	3
Constipation	1	3	4
Tinnitus	1	4	2
Vertigo	2	3	4
Headache	4	2	1
Rash	1	6	4
Oedema	1	1	4
Total	19	31	23

Discussion

In this study a new preparation of Naproxen used as suppositories has been shown to be more effective than placebo and as effective as Indomethacin suppositories. This is judged by reduction of early morning stiffness. Pain relief favoured Indomethacin. In terms of patient preference the two drugs appeared to be very similar.

There is a group of patients who prefer suppositories to capsules and Naproxen suppositories would seem to offer an alternative treatment to Indomethacin suppositories. It would appear to have advantage over that drug in terms of side

effects but slightly lower efficacy. Patient preference was similar for the two drugs. It may be seen as a useful alternative treatment.

References

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