Indomethacin or sulindac at night in rheumatoid arthritis

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Summary

The effects of indomethacin and sulindac in relieving troublesome morning stiffness and nighttime pain were tested in a double-blind cross-over trial. Thirteen of the 17 patients who completed the trial preferred indomethacin which was found to be superior to sulindac in all the parameters tested. Sulindac did, however, have some beneficial effect and can be used as an alternative to indomethacin when this drug cannot be used as the agent of first choice.


Various drugs have been used in patients with rheumatoid arthritis in order to relieve the common problems of sleep disturbances and early morning stiffness. Even when daytime symptoms are well-controlled with other non-steroidal anti-inflammatory drugs, night and early morning problems are still very common.

Indomethacin (Indocid, MSD) has been the standard drug used in this regard. Suppositories of 100 mg were initially used, but Huskisson et al.1 showed that the same dose of oral indomethacin was more effective than the suppository. Indomethacin has also been shown to be superior to diazepam in relieving stiffness,2 and superior to amylobarbitone for inducing sleep in rheumatoid arthritis.3 Evening corticosteroid therapy is often used as an alternative method of relieving the problem of morning stiffness.4,5 Other anti-inflammatory drugs have also been used as alternatives to indomethacin. Sulindac (Clinoril; Frost-MSD) is the agent which is closest, chemically, to the structure of indomethacin6 and is reported to have a similar method of action.7 Because of possible effects on the gastrointestinal and central nervous system with indomethacin, especially in older patients, it was decided to compare the two agents administered as a single night-time dose, in addition to the other anti-inflammatory or general medication being used.

Patients and methods

Twenty outpatients with classic or definite rheumatoid arthritis8 were studied. The patients, 15 females and 5 males, were between 41 and 68 years of age and had suffered from rheumatoid arthritis for between 1 and 30 years (mean 11.0 years). They all experienced morning stiffness of at least 30 minutes’ duration. Patients were excluded if they were receiving systemic corticosteroids, penicillamine, gold or antimalarial drugs, or more than 75 mg indomethacin per day in divided doses. Previous sensitivity to indomethacin or peptic ulceration were also considered as contraindications.

The patients were maintained on their regular therapy throughout the period of the study, which was 6 weeks. Physiotherapy and occupational therapy were continued if deemed necessary. The trial was a double-blind cross-over study, and patients received indomethacin 75 mg or sulindac 100 mg at night. The patients received each drug for 3 weeks. All patients were fully examined at the beginning of the trial and were assessed at weeks 3 and 6. At each visit a Ritchie count was done and night and morning pain were measured on a 10 cm visual analogue scale. Duration of morning stiffness was measured in minutes and the patients were asked to describe the effect of the drug on their sleeping pattern. The clinician and patient made an assessment of response to treatment on a four-point scale (no effect, slight effect, good effect, excellent). At every visit a blood sample was taken in order to assess the haemoglobin concentration, white cell count, erythrocyte sedimentation rate, rheumatoid factor and alkaline phosphatase.
level, as well as a urine sample in order to test for the presence of blood, albumin and sugar.

Results

Twenty patients took part in the trial. Three patients withdrew — 2 while taking sulindac (1 because of severe gastric pain and 1 owing to oedema of the legs) and 1 while taking indomethacin (owing to heartburn, nausea and epigastric pain). These side-effects cleared completely on withdrawal of the drug. During the period of observation there were no significant changes in the haemoglobin concentration, erythrocyte sedimentation rate, rheumatoid factor or any other biochemical parameters that were tested. The patients' preferences were as follows: 13 preferred the indomethacin treatment; it should be noted that 3 of these patients also felt an improvement in their symptoms while taking sulindac, and 4 preferred the sulindac treatment.

Assessments of the duration of morning stiffness were made at weeks 3 and 6 and compared with the duration before the trial began (week 0 — control value 79.1 min). There was a mean reduction of 51.7 (1 SD = 59.3) minutes in morning stiffness while the patients were taking indomethacin compared with 30.9 (1 SD = 51.2) minutes while they were on sulindac. The difference between the reduction in morning stiffness in the two groups was statistically significant ($P < 0.01$). When compared with the pre-treatment values, indomethacin caused a greater reduction in morning stiffness than sulindac ($P < 0.0005$), but sulindac was also found to cause a statistically significant reduction ($P < 0.05$). The 13 patients who preferred indomethacin had a mean reduction in morning stiffness of 68.5 ± 55.5 minutes, while the 4 who preferred sulindac had a mean reduction of 33.8 ± 27.0 minutes. This difference is not statistically significant, probably owing to the small number of patients in the sulindac group. Both drugs reduced the amount of pain suffered by the patients during the day and at night. The reduction was greatest while the patients were taking indomethacin.

The improvement in the pain scale for morning and evening pain is shown in Table I. Again, the values for weeks 3 and 6 were subtracted from the baseline value of week 0. Both morning and evening pain were statistically significantly more reduced while the patients were taking indomethacin, but there was also a reduction with sulindac. Of the 13 patients who preferred indomethacin, 10 reported an improvement in the quality of their sleep. Three had no change in their sleeping patterns, which were not interrupted before the trial. Of the 4 patients who preferred sulindac, 2 had slept well before the trial was commenced and 2 noted an improvement in their sleep pattern. Side-effects were reported by 5 patients, 3 while on indomethacin and 2 while on sulindac. Two patients on indomethacin reported headache and 1 nausea, while both patients on sulindac reported some upper abdominal pain and slight nausea. Treatment was continued despite these side-effects and they disappeared after the drug was withdrawn.

Discussion

Despite the fact that sulindac is chemically related to indomethacin, at the dosages used in this trial it was found that indomethacin was more helpful in relieving pain at night and aiding morning stiffness. Various studies have shown that sulindac is superior to aspirin in the relief of daytime pain and of morning stiffness. Sharma and Haslock, however, showed that a combination of indomethacin and diazepam was superior to sulindac 200 mg alone, or sulindac with diazepam (10 mg). Differences in this study were not statistically significant, but the two sulindac regimens were almost as efficacious as the indomethacin-diazepam combination. These studies used a single-dose crossover technique, and the results might not be appropriate in predicting long-term effects and the side-effects of different drugs or combinations of drugs. In addition, the majority of patients noted that their sleep was less disturbed and that they were awake less during the night. This is a contrast to the results of Murthy et al. who found that neither indomethacin nor prednisolone affected the quality of sleep in their group of patients, but noted that most of their patients had been sleeping well before the study began.

In the present study there was a statistically significant reduction in the duration of morning stiffness while the patients were taking both indomethacin and sulindac, but the reduction was far greater with indomethacin alone. The incidence of side-effects in the 2 groups was similar, with 2 patients withdrawing because of gastro-intestinal problems, 1 on indomethacin and 1 on sulindac. One patient withdrew because of oedema of the legs while taking sulindac. Apart from 1 patient who complained of slight headache, there were no central nervous side-effects — a common problem when indomethacin is taken during the day.10 There were no changes in the biochemical parameters tested. Even though indomethacin was far more effective than sulindac in relieving the symptoms of rheumatoid arthritis, sulindac did have a beneficial effect, and can be used as an alternative to indomethacin when this drug cannot be used.

TABLE I. IMPROVEMENT IN PAIN SCALE (cm) IN 17 PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Morning pain</th>
<th>Evening pain</th>
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</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>2.11</td>
<td>0.89</td>
</tr>
<tr>
<td>Sulindac</td>
<td>2.15</td>
<td>0.97</td>
</tr>
<tr>
<td>SD</td>
<td>2.4</td>
<td>2.8</td>
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<tr>
<td>* $P &lt; 0.05$</td>
<td>* $P &lt; 0.05$</td>
<td>* $P &lt; 0.05$</td>
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</tbody>
</table>

* Paired t tests.

REFERENCES