Night-time indomethacin in rheumatoid arthritis

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Summary

Indomethacin is commonly prescribed at night to relieve morning stiffness in patients with rheumatoid arthritis. Pharmacokinetic and pharmacodynamic interactions are frequently described with non-steroidal anti-inflammatory drugs, and the rationale for using more than one of these agents at the same time is questionable. A randomized crossover trial was carried out in 14 patients to compare the effects of 100 mg indomethacin at night with those of placebo when added to a baseline regimen of stabilized salicylate therapy with a slow-release preparation. Each treatment was given for 2 weeks. The results suggest that the addition of indomethacin produced no significant benefit in terms of reduction in the duration of morning stiffness or on the overall daily pain score.

Key words: Indomethacin — aspirin — arthritis, rheumatoid

Introduction

Indomethacin and aspirin are commonly prescribed together for the treatment of chronic rheumatoid arthritis. Pharmacokinetic interactions have been reported between indomethacin and aspirin, and a clinical study has also failed to demonstrate increased efficacy of indomethacin and aspirin taken together over either drug used alone. Indomethacin, however, is often prescribed at night to patients on a salicylate regimen in an effort to reduce night pain and the duration of morning stiffness. There is no doubt that indomethacin taken by suppository, or by the oral route, is useful in reducing morning stiffness in patients with rheumatoid arthritis and it has been clinical practice to add indomethacin to a salicylate regimen in an effort to try and combat this common problem of morning stiffness.

The new enteric-coated or sustained-release aspirin preparations show stable salicylate levels throughout a 24-hour period on a twice daily regimen. We decided, therefore, to study the effect of 100 mg indomethacin, given orally at night, on the duration of morning stiffness in patients with rheumatoid arthritis stabilized on maximum doses of a sustained-release aspirin preparation (SRA, Boots).
Patients and methods
Twenty-one patients with seropositive rheumatoid arthritis entered the study. The mean age of the patients was 49 years, and the mean duration of rheumatoid arthritis was 4.5 years. Seven patients were also taking disease suppressive drugs (2 on gold and 5 on D-penicillamine) but had been stabilized on therapy for at least 1 year.

The study design consisted of three 2-week treatment periods. The initial 2 weeks was for stabilization on salicylate where the dose of salicylate was increased until tinnitus occurred. The dose of salicylate was then reduced by 1 tablet per day. At the end of the 2-week stabilization period, patients were allocated in a random order to 2-week treatment periods of 100 mg indomethacin at night or identical indomethacin placebos. At the end of the 2-week treatment period patients were crossed over to the other regimen. The salicylate dosage was maintained throughout the study.

A pain score and morning stiffness chart was filled in daily by each patient and the patient was seen for assessment on the last day of each treatment period. Patients were seen at the same time of the morning 12 hours after their last dose of salicylate. At that time, blood was withdrawn for salicylate estimation. The serum salicylate was measured in duplicate by the method of Trinder.

Results
Of the 21 patients who entered the trial, 5 patients dropped out during the first fortnight because of failure of salicylate to suppress pain and stiffness, and 2 patients dropped out during the rest of the study due to lightheadedness and headaches when taking indomethacin. Statistical analysis, therefore, was performed on 14 patients finishing the 4-week crossover period of indomethacin or indomethacin placebos. The mean pain score and mean duration of morning stiffness was taken as the average daily score during the second week of each treatment period.

The results are summarized in Table 1 and it can be seen that there was no significant difference between the mean daily pain score and the mean duration of morning stiffness on either regimen. The duration of morning stiffness was slightly less when indomethacin was added to the treatment regimen, but not significantly so. Salicylate levels taken 12 hours after the last dose were not significantly different on either regimen, but were just in the recommended therapeutic range for salicylate concentrations (150 to 300 μg/l).

Discussion
In this small number of patients we have failed to show a significant decrease in the duration of morning stiffness when indomethacin is added to a regimen of maximal salicylate therapy. The sustained-release aspirin preparation used produces a slow absorption phase over a 6 to 8-hour period, and at doses used
Table 1. Daily pain score, duration of morning stiffness and morning salicylate level in patients with rheumatoid arthritis: mean (+S.D.) values

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Salicylate</th>
<th>Salicylate plus indomethacin</th>
<th>Salicylate plus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score (n=14)</td>
<td>2.4±0.8</td>
<td>2.7±0.9</td>
<td>2.6±1.1</td>
</tr>
<tr>
<td>Duration of morning stiffness (hours) (n=14)</td>
<td>2.9±1.9</td>
<td>2.3±1.8</td>
<td>2.9±1.8</td>
</tr>
<tr>
<td>Salicylate level (µg/l) (n=10)</td>
<td>188±52</td>
<td>193±43</td>
<td></td>
</tr>
</tbody>
</table>

in rheumatoid arthritis the salicylate t½ approaches 16 hours. This means that plasma and presumably synovial fluid levels of salicylate are maintained at a fairly constant rate throughout a 24-hour period.

Side-effects have been shown to be more frequent when indomethacin and aspirin are taken together, and this, coupled with our results, would suggest that there is no significant benefit to be gained from the combined regimen. Although indomethacin taken at night does reduce the duration of morning stiffness, its use in our patients did not produce a significant reduction and it had no effect on the overall daily pain score.

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References