Nimesulide in the Short-Term Treatment of Osteoarthrosis: A Pilot Study for Assessing the Minimal Effective Dose

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Eleven patients suffering from osteoarthritis of the cervical spine were admitted to a pilot study aimed at establishing the effective dose and the tolerability of Nimesulide.

The patients received a basic treatment of Nimesulide 100 mg/day, increasable up to 300 mg/day, in conformity with the patient's need. The treatment over a period of 15 days showed that Nimesulide 200 mg/day has good anti-inflammatory and analgesic properties. Several critical parameters were significantly improved. The incidence of usually mild side-effects was very low.

Introduction

Osteoarthritis is a slowly evolving degenerative articular disease characterized by the gradual development of joint pain, stiffness and limitation of motion (Moskowitz 1972).

Since inflammation may play a role even in this form of arthritis (Hart 1975, Dieppe, Huskisson & Willoughby 1980), the use of non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis seems to be justified, especially when such drugs display a satisfactory anti-inflammatory effect.

As therapeutic effects are rarely achieved without undesirable and sometimes severe side-effects (Cuthbert 1974), there is a definite need of effective and safe anti-inflammatory analgesic drugs for rheumatic pain (Leading Article, British Medical Journal 1976). Therefore, any new compound belonging to this class deserves to be tested.

Nimesulide is a new non-steroidal anti-inflammatory drug. It is the 4-nitro-2-fenoximetansulfonanilide.

It has proved its good anti-inflammatory, analgesic and antipyretic activity in animal models (Grant, Moore & Swingle 1975).

It is well tolerated and has no cardiovascular or nervous system toxicity (Various, Biex Solaris File 1976).

On the basis of several in vitro studies, the anti-inflammatory activity of Nimesulide is believed to be related to an inhibition of prostaglandin synthetase systems (Vigdahl & Tukey 1977, Vigdahl & Tukey 1975). This inhibitory activity is shared with most of the known non-steroidal anti-inflammatory drugs, including aspirin and phenylbutazone.

Preliminary results obtained from clinical trials in patients with rheumatic diseases seem to indicate that Nimesulide is active and well tolerated (Weissenbach 1981, Gamarski 1981). Nevertheless, the therapeutic schedule has not been well determined until now.

The present open study was aimed at establishing the effective dose and the tolerability of Nimesulide in a sample of patients suffering from chronic osteoarthritis.
Michele Reiner

Material and Methods

Eleven out-patients (nine females and two males) with osteoarthritis of the cervical spine, aged from 39 to 87 years (average 60·18 years), regularly attending the hospital, were admitted to the trial. They were reliable and collaborative persons, who gave their oral informed consent.

All of them had a roentgenologic evidence of degenerative disease, grades 2-4 measured by referencing to the Atlas of Standard Radiographs of Arthritis (Council for International Organizations of Medical Sciences 1963). They had the disease for a mean of 7·5 years and were presently experiencing pain on motion and tenderness of the affected joint, and limitation of movement.

Subjects with kidney or liver disorders, overt or suspect gastro-intestinal disease, and/or suffering from other diseases which might affect the joints were excluded. Other exclusion criteria were history of idiosyncratic or allergic response or known intolerance to non-steroidal anti-inflammatory drugs.

Former treatments were stopped 1 or more weeks before starting the trial: 1 week for non-steroidal anti-inflammatory drugs (NSAIDs) and not less than 4 weeks for glucocorticoids. Other treatments with NSAIDs and analgesics were not allowed during the study.

A brief description of the patients is given in Table 1.

This open trial was carried out during a 3-month period (from July to September).

The patients received a basic treatment of Nimesulide 50 mg tablets, twice-a-day, for up to 20 days.

In conformity with the patients’ need, at any time, the investigator was allowed to increase the daily dose up to 300 mg and to decrease it back to the basic treatment.

Five patients were asked to consume the daily dose before meals and six patients after meals.

Table 1

Patient sample with cervico-arthrosis admitted to the trial

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Patient initials</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>Height (cm)</th>
<th>Diagnosis</th>
<th>First diagnosis</th>
<th>Concomitant diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MM</td>
<td>F</td>
<td>48</td>
<td>60-0</td>
<td>162</td>
<td>Cervico-arthrosis</td>
<td>1974</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>BA</td>
<td>F</td>
<td>64</td>
<td>69-5</td>
<td>163</td>
<td>&quot;</td>
<td>1977 Coronary deficiency</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>GN</td>
<td>F</td>
<td>73</td>
<td>57-0</td>
<td>151</td>
<td>&quot;</td>
<td>1960</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>GE</td>
<td>F</td>
<td>67</td>
<td>57-0</td>
<td>146</td>
<td>&quot;</td>
<td>1962 Osteoporosis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KE</td>
<td>M</td>
<td>87</td>
<td>59-0</td>
<td>168</td>
<td>&quot;</td>
<td>1970 Angina</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>GY</td>
<td>F</td>
<td>69</td>
<td>51-5</td>
<td>160</td>
<td>&quot;</td>
<td>1976</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>VC</td>
<td>M</td>
<td>56</td>
<td>74-0</td>
<td>171</td>
<td>&quot;</td>
<td>1974 Paget's syndrome</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>TC</td>
<td>F</td>
<td>42</td>
<td>56-0</td>
<td>156</td>
<td>&quot;</td>
<td>1976</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>BD</td>
<td>F</td>
<td>56</td>
<td>65-0</td>
<td>160</td>
<td>&quot;</td>
<td>1975 Hyperlipaemia, ischaemic and hypertensive cardiopathy</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NB</td>
<td>F</td>
<td>61</td>
<td>101-0</td>
<td>160</td>
<td>&quot;</td>
<td>1978 Anxious depression, obesity, urinary infection</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CG</td>
<td>F</td>
<td>39</td>
<td>62-0</td>
<td>157</td>
<td>&quot;</td>
<td>1975 Obesity</td>
<td></td>
</tr>
</tbody>
</table>
At each visit the patients were always assessed by the same physician at about the same hour of the day.

The treatments' efficacy was evaluated by means of the following parameters:
(a) Spontaneous pain, pain severity on passive and active motion, assessed by the patients on a 5-point scale, where:
0 = absent
1 = slight
2 = moderate
3 = severe
4 = very severe
(b) Quality of sleep based on its duration and on the patients' subjective feeling of fitness on awakening, assessed on a 5-point scale where:
0 = very poor
1 = poor
2 = fair
3 = good
4 = very good
(c) Duration of morning stiffness (in minutes), after rising in the morning.
(d) Range of motion of the cervical spine measured with a goniometer except for leaning forwards which was measured as the shortest distance from the chin to the sternum.
(e) Patient's and investigator's opinion on efficacy was scored as follows:
- 1 = deterioration
0 = no change
1 = moderate improvement
3 = improvement
4 = marked improvement

The patients were provided with diary cards for recording side-effects and drug consumption.

Wilcoxon's signed-rank test for paired data was used for the comparison amongst the clinical index values found before, during and after treatment.

Analysis of the range of motion and the morning stiffness determination was effected by the paired sample 't' test.

Results
Nine patients completed a treatment period of at least 10 days. Two out of these nine patients were treated for up to 20 days.

For all patients, the initial dose of Nimesulide was 100 mg/day (50 mg twice a day). The average daily dose was 156.69 mg; the average maintenance dose, calculated from the 5th day up to the study-end, was 159.94 mg per day (Figure 1).

Mean value of signs and symptoms observed before and during the treatment period is shown in Table 2.

Spontaneous pain, pain on movement, poor quality of sleep, stiffness and marked limitation in the cervical spine motion were found in patients when entering the trial.

The speed of onset of action, when Nimesulide was given to the eleven patients with pain, is shown in Figure 2. After 1 day of treatment there were significant decreases compared with basal values (p < 0.05). These clinical improvements were most marked after 5 and 10 days of treatment, up to the complete disappearance of symptoms at the last assessment (p < 0.01).

The average duration of morning stiffness before the commencement of treatment was

![Fig 1 Dosage schedule in eleven patients with cervico-arthrosis admitted to the trial](imr.sagepub.com)

- 100 mg/day
- 200 mg/day
- 300 mg/day

<table>
<thead>
<tr>
<th>Patient n.</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td></td>
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<tr>
<td>10</td>
<td></td>
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<tr>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
Table 2

Average ± S.E.M. of spontaneous pain, pain severity, quality of sleep, duration of stiffness and range of motion assessed at the beginning of the trial, after 1, 5, 10 and 15 days of treatment

<table>
<thead>
<tr>
<th></th>
<th>At the beginning of the trial</th>
<th>Days of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Spontaneous pain (Score 0–4)</td>
<td>2·18 ± 0·26</td>
<td>1·27 ± 0·27●</td>
</tr>
<tr>
<td>Pain severity on motion (Score 0–4)</td>
<td>2·90 ± 0·18</td>
<td>2·00 ± 0·30●</td>
</tr>
<tr>
<td>Active</td>
<td>2·40 ± 0·22</td>
<td>1·40 ± 0·27●</td>
</tr>
<tr>
<td>Quality of sleep (Score 0–4)</td>
<td>1·64 ± 0·31</td>
<td>2·36 ± 0·20●</td>
</tr>
<tr>
<td>Morning stiffness (duration, min.)</td>
<td>65·62 ± 18·36</td>
<td>31·87 ± 8·16●</td>
</tr>
<tr>
<td>Torsion</td>
<td>39·54 ± 2·07</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>38·64 ± 2·24</td>
<td>—</td>
</tr>
<tr>
<td>Flexion</td>
<td>30·91 ± 2·41</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>28·64 ± 1·79</td>
<td>—</td>
</tr>
<tr>
<td>Leaning forward (cm)</td>
<td>2·80 ± 0·80</td>
<td>—</td>
</tr>
<tr>
<td>Extension</td>
<td>35·00 ± 3·41</td>
<td>—</td>
</tr>
</tbody>
</table>

Significance of differences before and after 1, 5, 10 and 15 days estimated by the Wilcoxon Signed-Rank Test for Paired Data. Paired Sample 't' Test for morning stiffness and range of motion. p Values: ● = < 0·05; ●● = < 0·01
about 60 minutes (ranging from 30 to 180 minutes). From the 1st day of treatment a highly significant improvement was observed, decreasing morning stiffness by more than 50%. At the 5th day of treatment, the duration of morning stiffness had decreased to 15 minutes, and after 15 days of therapy the symptom had disappeared.

All patients reported an improvement in the quality of sleep (p < 0.05) from the first day of treatment compared to baseline. This marked improvement was significant during the early phase of treatment and all patients derived some therapeutic benefit.

The assessment of the ability to function measured by the range of motion of the cervical spine, showed a consistent pattern of increasing mobility throughout the duration of the study. All patients reported functional improvement within the first 5 days of treatment and improved significantly up to the end of the trial (Figure 3).

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**Fig 2** Per cent variations in respect to the basal values (0) of spontaneous pain, morning stiffness and quality of sleep occurring after one (1), five (2), ten (3), and fifteen (3) days of treatment with Nimesulide.

**Fig 3** Per cent variations in respect to the basal values (0) of motion range occurring after five (1), ten (2) and fifteen (3) days of treatment with Nimesulide.
The patients’ global impression was one of improvement and greater facilitation in motion in nine cases, and this was confirmed by the physicians’ evaluation.

In general, Nimesulide was well tolerated. Four patients reported adverse reactions during the treatment: one patient had moderate and transient skin rash; one patient had heartburn, but its symptomatology disappeared as the drug was given after meals; one case of urticaria had to give up the treatment (200 mg/day) after 4 days, but this effect had been observed previously, during a treatment with other anti-inflammatory drugs; one patient stopped after 4 days (300 mg/day) because of gastralgia and vomiting.

Discussion
The idea that in osteoarthritis a fair correlation between the subjective symptoms and the objective signs might be observed, seems to be supported by joint symptoms and the extent and degree of the radiographic changes observed in the trial’s patient sample.

The patients’ assessment of pain severity and tenderness as well as the quality of sleep has been proved to be a sensitive parameter in evaluating the changes induced by the treatment. Thereafter, the goniometer used for the objective measurement of the cervical spine motion range has proved to be an effective and simple instrument.

We recognize that drug therapy plays a major role in the rehabilitative process of patients with osteoarthritis and that the selection of the proper therapy requires a thorough examination of data in a large number of patients who have been receiving the drugs for extended periods.

This open study with Nimesulide, in a limited number of osteoarthritic patients, had the sole purpose of assessing the short-term clinical value of the drug in the management of this disease and of establishing the effective dose.

Treatment with Nimesulide over a period of 15 days has confirmed the activity of the compound both by subjective and objective criteria. The latter have shown some limitations too.

In fact, for patients suffering from a chronic condition such as osteoarthritis, with a more or less profound anatomical deterioration, frequently there is not much room for a functional improvement after a treatment which cannot be expected to modify or revert the underlying cause of the disease. Therefore, such things are not expected to be modified by the treatment as much as the intensity of pain or of tenderness.

Only four patients were treated with 100 mg/day; they did not require any alteration of the drug schedule, and obtained benefit from the therapy.

The remaining patients were given 200 mg/day and, in three cases, 300 mg/day. Moreover, the mean daily dose was higher than 100 mg/day, being about 160 mg/day for each patient.

During treatment with Nimesulide four patients experienced side-effects and two patients had to give up the drug. Even though no relationship was found between an increase of side-effects and the mean daily dose, one patient experienced nausea and vomiting only with 300 mg/day. In conclusion, the preliminary results of this pilot study seem to indicate that Nimesulide 200 mg/day is effective in controlling the symptoms of osteoarthritis and in improving some objective parameters of the disease. The other dosage schedules tested (100 and 300 mg/day) were not found to be equally useful in this condition.

Further controlled clinical trials seem warranted for a better assessment of the therapeutic potential of this new anti-inflammatory compound.

Acknowledgements
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