Double-blind multicentre UK hospital studies of isoxicam vs naproxen

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- 1 Two multicentre, parallel group, randomised, double-blind, double-dummy comparison studies were conducted between isoxicam in the usual dose of 200 mg once daily and naproxen 500 mg twice daily.
- 2 The drugs were administered for 4 weeks to 230 patients suffering from osteoarthritis of the hip and/or knee in the first trial and to 249 patients suffering from rheumatoid arthritis in the second.
- 3 The studies compared treatments for both safety and overall effectiveness in the relief of pain.
- 4 In the osteoarthritis trial, overall pain was reduced by both drugs after 2 weeks of therapy but only isoxicam produced further improvement after 4 weeks.
- 5 Isoxicam produced reductions comparable to those produced by naproxen in pain on standing from the sitting position, pain on walking, and pain on movement of the affected joint, after 2 and 4 weeks.
- 6 After 4 weeks, isoxicam given once daily in the morning was significantly more effective than naproxen given in the morning and the evening in relieving not only total pain as assessed by a visual analogue scale but, as importantly, night pain.
- 7 Compared to naproxen therapy, isoxicam therapy was associated with significantly more patients whose disease state was improved at 2 weeks, as assessed by physicians.
- 8 In the rheumatoid arthritis trial, isoxicam was equally as effective as naproxen in reducing joint tenderness, joint swelling, and pain; at 4 weeks there was a trend in favour of isoxicam in reduction of joint swelling and pain.
- 9 Isoxicam reduced morning stiffness significantly more than naproxen after 4 weeks; this trend was apparent at 2 weeks.

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10 Patients thought that isoxicam was more effective than naproxen, to a significant difference.

11 In both trials, the two drugs were well tolerated and had similar side effects profiles, with the majority of adverse experiences being associated with the digestive system; no side effect was severe.

Keywords isoxicam naproxen osteoarthritis rheumatoid arthritis pain

Introduction

Isoxicam is a new non-steroidal anti-inflammatory drug (NSAID) of the oxycam class with demonstrated analgesic, anti-inflammatory and antipyretic properties in animal models (Yakatan, 1982) and proven clinical efficacy and safety in osteoarthritis and rheumatoid arthritis (Downie *et al.*, 1984).

The elimination half-life of isoxicam is approximately 31 h in both young and elderly subjects, permitting it to be administered in a once-daily regimen for all age groups (Downie *et al.*, 1984). The constancy of the half-life of isoxicam throughout the adult lifespan is reflected in its equally good tolerance in both young and elderly patients, as observed in clinical studies (Haslock, 1984).

Isoxicam has been shown to be at least as effective and, in some instances, superior to other NSAIDs such as indomethacin, piroxicam, diclofenac, aspirin, and indomethacin for osteoarthritis and/or rheumatoid arthritis (Berry *et al.*, 1984; Downie *et al.*, 1984; Keegan, 1984; Parrino, 1984).

This paper reports two UK multicentre trials comparing isoxicam and naproxen in 479 patients: 230 with osteoarthritis and 249 with rheumatoid arthritis. The aim of these trials was to compare the effectiveness and safety of the usual dose of isoxicam of 200 mg given once daily with naproxen 500 mg given twice daily.

Methods

Osteoarthritis trial

Two hundred and thirty patients suffering from osteoarthritis of the hip and/or knee were selected by 16 rheumatologists at hospitals throughout the UK for inclusion in the trial. For admission, patients had to be over 18 years of age, admit to pain in the affected joint or joints severe enough to warrant treatment with NSAIDs, and had to have X-ray evidence of loss of joint space, osteophyte formation, or subchondral cysts.

Exclusion criteria included pregnancy or likelihood of becoming pregnant, other joint disease, past or present peptic ulcer, chest, kidney or liver disease, a history of allergy to an NSAID, anticoagulant therapy, therapy with another NSAID, an intra-articular injection of a steroid within 6 weeks prior to inclusion in the trial, or unstable physiotherapy status. Patient characteristics are indicated in Table 1.

The trial consisted of a 3-day wash-out period, followed by a 4-week, parallel, randomised, double-blind, double-dummy comparison of isoxicam 200 mg once daily and naproxen 500 mg twice daily. A continuation, 12 week open evaluation of isoxicam 200 mg daily will be reported at a later date.

Patients were assessed by the physicians at the end of the wash-out period and again after 2 and 4 weeks of treatment. Both visual and verbal assessments were made by the patients. The degree of pain was measured on 10 cm visual analogue scales ('no pain'–'as bad as it can be') and verbal assessments were made by the patient of pain experienced when standing from a sitting

Table 1 Osteoarthritis trial patient characteristics

Sex	Female	Male
Isoxicam	79	34
Naproxen	78	39
<i>Mean age (years)</i>		
Isoxicam (<i>n</i> = 113)	63.1	
Naproxen (<i>n</i> = 117)	62.3	
<i>Mean weight (kg)</i>		
Isoxicam (<i>n</i> = 112)	72.5	
Naproxen (<i>n</i> = 115)	71.9	
<i>Mean duration of osteoarthritis (months)</i>		
Isoxicam (<i>n</i> = 108)	74.0	
Naproxen (<i>n</i> = 115)	80.9	
<i>Joint affected</i>	<i>Hip</i>	<i>Knee Hip and knee</i>
Isoxicam	19	73 21
Naproxen	15	80 22

position, on walking, on passive movements of the affected joint and at night, as well as by rescue analgesic intake. Doctor and patient recorded both local and global response to treatment on a five-point and four-point scale, respectively.

Rheumatoid arthritis trial

Two hundred and forty nine patients with rheumatoid arthritis (RA) were entered into a 4 week, parallel randomised, double-blind comparison of isoxicam 200 mg once daily and naproxen 500 mg twice daily. The patients were selected by 19 consultant rheumatologists throughout the UK. One hundred and sixty eight patients had classical RA (84 received isoxicam and 84 naproxen) and 81 had definite RA (40 received isoxicam and 41 received naproxen). For entrance into the study, patients had to have six or more tender joints, three or more swollen joints, and an ESR of > 28 mm in 1 h. Exclusion criteria and trial design were similar to those for the osteoarthritis trial. Patient characteristics are indicated in Table 2.

Joint tenderness was measured according to the Ritchie articular index, joint swelling graded 0/3, pain assessed on a 10 cm visual analogue scale, and morning stiffness in minutes. The physician's and patient's overall assessments were made on a five-point scale and a global assessment on a four-point scale.

Additional information collected in both trials

Adverse experiences At each visit the patients were asked if anything unusual had occurred

since the last visit. Any adverse events volunteered by the patient or observed by the physician were recorded.

Laboratory tests Routine haematology (haematocrit, platelets, total white cell count—differential if abnormal, erythrocyte sedimentation rate), clinical chemistry (uric acid, blood urea, bilirubin, creatinine, alkaline phosphatase and one or more of ALT, AST and Gamma GT) and urine analysis (presence or absence of albumin, sugar and blood) were performed at the end of the washout period and after 2 and 4 weeks of treatment. Results were compared with laboratory normal values supplied by each investigator.

Statistical analyses The Mann-Whitney U-test was used to compare the naproxen and isoxicam groups of patients with respect to age, duration of disease, and weight. The chi-squared test was used to compare the numbers of women and men in the two groups. The Mann-Whitney U-test was used to compare the two groups with respect to the amount of rescue analgesics taken, pain as rated on the 10 cm visual analogue scale, articular index, joint swelling scores, and duration of morning stiffness and also to compare the two groups with respect to changes during treatment. The overall clinical assessments of the Rheumatoid Arthritis group, were grouped as, improved, the same or worse and the two treatment groups were compared using the chi squared test.

Results

Osteoarthritis trial

Two-hundred and thirty patients were entered into the trial; 113 were treated with isoxicam; and 117 with naproxen. One-hundred and ninety-five patients completed the 4 week double-blind phase. Eight patients failed to complete 4 weeks' treatment for reasons other than adverse events; and 27 because of adverse events, both treatment related and unrelated. Three further patients receiving naproxen were withdrawn at week 4, one of them for adverse events (see below).

The groups of patients were well matched with respect to sex, age, weight, duration of disease and joint affected (Table 1).

Table 2 Rheumatoid arthritis trial patient characteristics

Sex	Female	Male
Isoxicam	94	30
Naproxen	94	31
<i>Mean age (years)</i>		
Isoxicam (<i>n</i> = 124)	56.5	
Naproxen (<i>n</i> = 125)	57.3	
<i>Mean weight (kg)</i>		
Isoxicam (<i>n</i> = 124)	63.1	
Naproxen (<i>n</i> = 124)	66.0	
<i>Mean duration of disease (months)</i>		
Isoxicam (<i>n</i> = 122)	117.9	
Naproxen (<i>n</i> = 118)	120.2	

Pain relief

As assessed by the 10 cm visual analogue scales, pain was reduced by both isoxicam and naproxen after 2 weeks' treatment, but a further improvement occurred after 4 weeks in the isoxicam treated patients (Figure 1). The effect of isoxicam was significantly greater than that of naproxen after 4 weeks ($P < 0.05$). As assessed by verbal rating scales, pain was reduced by isoxicam and naproxen at both 2 and 4 weeks of treatment. However, isoxicam was significantly more effective than naproxen after 4 weeks' treatment with respect to pain relief at night ($P < 0.05$, Figure 2).

Both physicians' and patients' ratings of the osteoarthritis showed improvements after 2 and 4 weeks' treatment. However, the results of the physicians assessments after 2 weeks' treatment showed isoxicam to be significantly more effective than naproxen ($P < 0.05$). By 4 weeks the physicians assessments were similar for both drugs. The majority of patients in both groups did not require extra analgesics (such as paracetamol and dextropropoxyphene/paracetamol) and there was no difference between the two groups.

Adverse experiences

Twenty-four patients were withdrawn from the study due to adverse experiences (13 on isoxicam and 11 on naproxen). The most common adverse events involved the gastrointestinal tract; the two drugs had a similar side effect profile. Isoxicam and naproxen had comparable effects on laboratory tests. Twenty-nine patients treated with

Figure 1 Visual analogue pain scales on entry to the trial, at 2 weeks and at 4 weeks in patients treated with isoxicam (▨) or naproxen (□). The left-hand end of the scale (0 cm) reads 'no pain' and right-hand end of the scale (10 cm) reads 'as bad as it can be'.

Week 2	Worse	Same	Better
Isoxicam	14	41	45
Naproxen	10	51	39
$P = 0.065$ (χ^2 test)			
Week 4	Worse	Same	Better
Isoxicam	12	36	52
Naproxen	11	53	36

Figure 2 Changes in night pain compared with baseline assessments. The numbers in each bar refer to the percentage of patients deteriorating, remaining the same or improving.

isoxicam showed a rise in blood urea values compared with 22 treated with naproxen.

Rheumatoid arthritis trial

Two-hundred and forty-nine patients were entered into the trial; 124 were treated with isoxicam and 125 with naproxen. Two-hundred and eighteen patients completed the 4 week double-blind phase. Nine patients failed to complete 4 weeks' treatment for reasons other than adverse events and one patient was withdrawn at week 4. Twenty two patients failed to complete 4 weeks' treatment because of adverse events, both treatment related and treatment unrelated. Three further patients, two on isoxicam and one on naproxen, were withdrawn due to adverse events at week 4.

The two groups of patients were well matched with respect to sex, age and duration of disease. The patients receiving naproxen were slightly heavier but this difference was not statistically significant (Table 2).

Pain control

As assessed by the 10 cm visual analogue scales, pain was reduced by both isoxicam and naproxen after 2 and 4 weeks' treatment. The difference between isoxicam and naproxen was not statistically significant, but there was a trend favouring isoxicam ($P = 0.19$ after 2 weeks and $P = 0.08$ after 4 weeks).

Joint tenderness and swelling

Both drugs were effective in reducing the total joint swelling score. The difference between

isoxicam and naproxen was not statistically significant but there was a trend favouring isoxicam ($P = 0.19$ after 2 weeks and $P = 0.08$ after 4 weeks).

Morning stiffness

Both drugs reduced the duration of morning stiffness but isoxicam was significantly more effective than naproxen after 4 weeks' treatment ($P = 0.04$).

Overall assessment in rheumatoid arthritis

Both physicians' and patients' ratings of the rheumatoid arthritis showed improvements after 2 and 4 weeks' treatment. There were no significant differences between the effects of the two drugs.

Global assessment of response to treatment

Isoxicam was rated as significantly more effective than naproxen by the patients ($P = 0.04$).

Analgesic usage

Extra analgesics, each as paracetamol or paracetamol/dextropropoxyphene were taken by about 50% of the patients in each group. Additional analgesic consumption did not differ significantly between the two groups.

Adverse experiences

Twenty-five patients were withdrawn from the study due to adverse experiences; 15 patients on isoxicam and nine on naproxen for treatment related side effects and one on isoxicam for a treatment unrelated adverse experience. Four

patients were withdrawn due to raised liver function tests. The changes were minor and values returned quickly to normal after stopping treatment. Fourteen patients treated with isoxicam showed a significant rise in urea values compared with 18 treated with naproxen.

Discussion

In these large UK based studies, isoxicam at a dose of 200 mg given once daily was shown to be as effective as naproxen, in what some might consider to be a high dose of 500 mg given twice daily. In patients with osteoarthritis of the hip and/or knee isoxicam was significantly more effective than naproxen in producing overall relief of pain and of night pain. In addition, it provided a more rapid improvement in the patients' overall condition as assessed by the physician in charge. The superior improvement in night pain brought about by isoxicam attests to its long duration of action when given once-daily in the morning. The results of the current study confirm the efficacy of isoxicam shown previously by Eberl (1982), Turi *et al.* (1983) and Du Lac de Fugeries (1984).

In patients with rheumatoid arthritis, isoxicam was significantly more effective than naproxen in reducing morning stiffness, which again accords with the long half-life of isoxicam. In addition, the patients' own overall assessment of response to treatment favoured isoxicam. Thus overall, isoxicam produced comparable benefits to naproxen and for some parameters was superior. These benefits were achieved with a convenient, once-daily dosing schedule that should aid in encouraging patients to comply with drug treatment. Both drugs were well tolerated and showed a similar profile of unwanted effects.

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