Double-blind randomized controlled trial of isoxicam vs piroxicam in elderly patients with osteoarthritis of the hip and knee

N. BELLAMY^{1,2}, W. W. BUCHANAN² & E. GRACE²

¹University of Western Ontario, London, Canada and ²McMaster University, Hamilton, Ontario, Canada

- 1 Fifty-seven elderly patients with primary osteoarthritis of the hip and knee were entered into a double-blind, randomized, controlled parallel group trial to compare the efficacy and tolerability of isoxicam (maximum = 200 mg day⁻¹) and piroxicam (maximum = 20 mg day⁻¹).
- 2 Clinical assessments were made following a 1 week NSAID-free washout period and at biweekly intervals during the next 6 weeks of active treatment.
- 3 The majority of patients in both groups experienced a clinically important and statistically significant therapeutic response.
- 4 No statistically significant between-group differences were noted with respect to drug efficacy.
- 5 One patient was withdrawn from the piroxicam group because of lack of effect, but there were no such withdrawals from the isoxicam group.
- 6 Five patients were withdrawn from the piroxicam group because of adverse reactions compared to only one withdrawal from the isoxicam group.
- 7 This study indicates that isoxicam is an efficacious and well-tolerated once-daily NSAID for elderly patients with osteoarthritis.

Keywords osteoarthritis isoxicam piroxicam elderly

Introduction

Osteoarthritis is primarily a disease of the elderly (Kellgren & Lawrence, 1958). Although many individuals have subclinical or pre-radiographic disease, the prevalence of symptomatic disease shows a positive correlation with chronologic age. Although primary osteoarthritis may affect the distal and proximal interphalangeal joints and the first carpometacarpal joints of the hands as well as the apophyseal joints of the axial skeleton and the first metatarsophalangeal joint of the toe, it is involvement of the hip and knee which results in the greatest discomfort and locomotor disability.

Since there are currently no disease-modifying anti-rheumatic drugs with which to treat osteoarthritis, the principal objective of therapy is to relieve pain and improve function. Thus the non-steroidal, analgesic anti-inflammatory drug remain the treatment of choice for patients with this disorder. The response to any given agent, varies between individuals and has in recent years resulted in the development of a number of new non-steroidal anti-inflammatory drugs (NSAIDs) (Rosenbloom *et al.*, 1985). The elderly in particular require an agent which is not only efficacious and well tolerated but also can

be taken according to a simple dosing regimen. There has been a steadily growing interest in studying therapeutic responsiveness and tolerability in elderly subjects since they represent a large proportion of the population with chronic musculoskeletal disease. Furthermore, they have a limited potential for response and demonstrate an increased propensity for developing adverse reactions to certain classes of drugs. In the report which follows, the efficacy and tolerability of isoxicam, a new NSAID, have been compared to those of piroxicam in a group of elderly patients with osteoarthritis of the hip and knee. Isoxicam has the chemical formula 4-hydroxy-2-methyl-N-(5-methyl-3-isoxolyl)-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide and is a benzothiazine derivative of the oxycam class of drugs (Yakatan, 1982). In addition to its comparative objectives, this trial was used to validate a new multidimensional outcome measure for clinical trials in osteoarthritis (Bellamy, 1982). The results of the validation study form the basis of a separate report and are not discussed in this paper.

Methods

The trial was conducted in two centres and employed a double-blind, randomized, controlled parallel design. Elderly patients with primary osteoarthritis of the hip and/or knee were enrolled in the study programme if they were 55–85 years of age and showed radiographic evidence of osteoarthritis. They were excluded if they had undergone prior replacement surgery on the joint of interest or had secondary osteoarthritis, active peptic ulceration or prior gastrointestinal bleeding. Other exclusion criteria included cardiorespiratory insufficiency, significant disease of any other major organ system, a BUN greater than 30 mg 100 ml⁻¹, SGOT greater than 50 units ml⁻¹, allergy to aspirin or other NSAIDs, concurrent anticoagulant therapy, or recent systemic or intra-articular corticosteroid therapy. Following enrollment, patients were assessed and randomized to receive either isoxicam or piroxicam according to a randomization code developed by an independent statistician. Thereafter patients underwent a 1-week NSAID-free washout period during which time analgesia with paracetamol (325 mg tablets) was permitted but monitored.

Following this washout period, baseline assessments were made and active treatment started with either isoxicam, 100 mg day⁻¹, or piroxicam, 10 mg day⁻¹ (Level 1). Each medica-

tion was identical in appearance and presented in capsule form. Patients were instructed to take the medication once daily with their breakfast and were advised against the concomitant use of salicylate-containing compounds during the study period. Patients were reassessed 2 weeks later and a decision made to continue at this treatment level or, if the response had been suboptimal, to increase the dosage to either isoxicam, 200 mg day⁻¹, or piroxicam, 20 mg day⁻¹ (Level 2).

Patients were again assessed 2 weeks later and a final assessment was made 2 weeks after that. The total period of active treatment was 6 weeks. The following outcome measures were employed, assessments being made at each of the four assessment points:

1. Night pain (four-point Likert scale (Nunnally, 1967))
2. Pain on walking (four-point Likert scale)
3. Degree of starting pain (four-point Likert scale)
4. Pain on joint motion (four-point Likert scale)
5. Joint tenderness (modified Doyle index) (Doyle *et al.*, 1981)
6. Knee total range of movement (degrees)
7. Intermalleolar straddle (cm)
8. Visual analogue scale of pain (vertical, 21-compartment, terminal descriptors only)
9. Physician overall assessment (five-point Likert scale)
10. Patient overall assessment (five-point Likert scale)
11. Walking time (50 feet)
12. Laboratory values: CBC, SMA-12, urinalysis.

Many patients had multijoint involvement but for each patient a single (either a hip or a knee) joint was identified as being more severely affected and was selected as the target joint for outcome measures numbers 1–7. In addition, the investigators recorded any adverse reactions to drug therapy and concurrent illness. At the final assessment (visit 4), both patients and physicians compared the efficacy and tolerability of the study drugs to both the drug-free washout period and their pre-study anti-inflammatory medication. During the course of the trial patients were allowed to take concomitant analgesia with paracetamol (325 mg tablets) although patients were instructed to use the tablets sparingly and their requirements were monitored. Compliance to the study medications was measured by both direct report and by pill count.

The analysis was conducted using an intention-to-treat philosophy rather than an explicative approach (Sackett & Gent, 1979). Thus withdrawals were accounted for in the analysis rather than being excluded from consideration. The following statistical tests were employed: chi square (Fleiss, 1981), Fischer's exact (Fleiss, 1981), unpaired two-tailed Student's *t*-test (Armitage, 1971), Mann Whitney U (for visual analogue and Likert-type scales) (Conover, 1980), and log rank chi square (for life table analysis (Friedman *et al.*, 1981).

Results

Of the 57 patients enrolled in the study, 28 received isoxicam and 29 received piroxicam. The mean age was exactly the same in each group (66.5 years) and the age ranges were similar (Table 1). Mean disease duration was slightly greater for isoxicam (9.3 years) than for piroxicam (8.7 years), but this difference was not statistically significant. Furthermore no significant differences were noted in the proportion of hips and knees represented in the two treatment groups, although in general the knee joint was frequently the more severely affected of the two joints. Males and females were represented in similar proportions although there was a slight female predominance in the piroxicam group (Table 1). Post-randomization group comparability was assessed at the end of the washout period. No statistically significant between-group differences were detected for any demographic or disease variable (Table 2).

In order to evaluate the response achieved at the initial level of therapy (i.e., isoxicam, 100 mg day⁻¹, or piroxicam, 10 mg day⁻¹) data were analyzed at visit 2 and compared with baseline values (Table 3). Significant improvements were noted in pain on joint movement, visual analogue scale for pain, and the physician's overall assessment in both groups. In the isoxicam group, significant improvement was also detected in pain on walking and patient overall assessment, while in the piroxicam group significant improvement was noted in night pain and joint tenderness.

Overall, both groups showed improvement at the initial level of therapy, although only six isoxicam and four piroxicam patients remained at this level (i.e., isoxicam, 100 mg day⁻¹, or piroxicam, 10 mg day⁻¹). A between-group comparison made at visit 3 showed no statistically significant difference other than in relief of pain on walking, which favoured the isoxicam group.

In order to assess response to the optimal dose, i.e., after any necessary dose titration, comparisons were made between visit 4 and baseline. Statistically significant improvement over baseline (Table 4) was noted in both treatment groups with respect to night pain, pain on walking, starting pain, pain on movement, joint tenderness, visual analogue scale of pain, overall assessment by physician, and overall assessment by patient. Although joint swelling in the knee declined in both groups (Table 2) a statistically significant response was achieved only in the isoxicam group (Table 4). Knee range of movement and intermalleolar straddle increased and the walking time decreased in both groups (Table 2) although none of these measures reached statistical significance in either group (Table 4). Between-group comparisons were made for all disease variables at visit 4 (i.e., after 6 weeks of active treatment); no significant differences were detected, indicating that the therapeutic response was similar in the two treatment groups (Table 4). One patient was withdrawn from the piroxicam group because of inefficacy; there were no such withdrawals from the isoxicam group. Compliance levels for study medications were exceptionally high both when measured by direct report and by pill count. Data collection on concomitant analgesia was incomplete and while no apparent between-group differences were noted no formal analysis could be performed.

Twelve adverse reactions in six patients were reported on isoxicam vs 24 adverse reactions in 12 patients on piroxicam (*P* = 0.105) (Table 5). Fluid retention, gastrointestinal upset and neurological symptoms accounted for the majority of adverse reactions. Reactions were graded by the investigators as being either mild, moderate or severe. Although five severe adverse

Table 1 Post-randomization – pre-intervention comparison of treatment groups

Variable	Isoxicam (n = 28)	Piroxicam (n = 29)	P value
Age (range) (years)	66.5 (55–80)	66.5 yrs. (55–82)	NS
Disease duration (years)	9.3 (1–26)	8.7 yrs. (1–30)	NS
Sex	14 male 14 female	12 male 17 female	NS
Most severely affected joint	7 hip 21 knee	11 hip 18 knee	NS

Table 2 Mean values for outcome variables at baseline and visits 2, 3 and 4. S.d. given for baseline values

		Baseline	Visit 2	Visit 3	Visit 4
Night pain	(I)	1.68 ± (0.72)	1.26	0.93	0.63
	(P)	1.83 ± (1.00)	1.25	1.19	0.77
Pain on walking	(I)	2.00 ± (0.82)	1.30	1.30	1.00
	(P)	2.14 ± (0.92)	1.86	1.36	1.05
Standing pain	(I)	1.39 ± (0.99)	1.04	0.78	0.65
	(P)	1.79 ± (1.11)	1.54	1.04	0.82
Pain on movement	(I)	1.57 ± (1.00)	1.04	0.59	0.52
	(P)	2.07 ± (0.75)	1.36	1.23	0.59
Joint tenderness	(I)	1.50 ± (0.92)	1.00	0.62	0.56
	(P)	1.89 ± (0.82)	1.04	0.91	0.55
Joint swelling (knee)	(I)	0.52 ± (0.75)	0.30	0.35	0.15
	(P)	0.94 ± (1.03)	0.59	0.65	0.38
Range of movement (knee) (°)	(I)	106.48 ± (22.17)	113.75	116.55	115.55
	(P)	102.44 ± (15.47)	106.24	106.88	109.50
Intermalleolar straddle (hip) (mm)	(I)	71.14 ± (27.01)	77.86	85.14	91.29
	(P)	60.00 ± (19.10)	60.20	67.63	74.17
Analogue scale of pain (mm)	(I)	13.71 ± (5.33)	8.85	7.41	6.19
	(P)	14.17 ± (5.34)	10.79	8.68	8.68
Overall assessment (MD)	(I)	3.44 ± (0.85)	2.67	2.46	2.15
	(P)	3.52 ± (0.87)	2.96	2.56	2.27
Overall assessment (patient)	(I)	3.48 ± (0.80)	2.70	2.54	2.26
	(P)	3.52 ± (0.83)	3.00	2.68	2.32
Walking time (s)	(I)	17.14 ± (8.26)	15.27	14.41	14.72
	(P)	15.25 ± (6.02)	15.96	15.90	14.39

I isoxicam, P piroxicam

reactions were noted on piroxicam, none of the reactions observed on isoxicam (Table 5) were graded as severe ($P = 0.03$). Furthermore, five patients were withdrawn from piroxicam due to adverse reactions compared to only one withdrawal from isoxicam (a moderate adverse reaction) ($P = 0.105$).

Thus, the total number of patients withdrawn due to either inefficacy or intolerance was six in

the piroxicam group and one in the isoxicam group. The ability of patients to stay in treatment was compared using a life table approach (Friedman *et al.*, 1981). Although the between-group differences were not statistically significant ($P > 0.05$), it can be seen from Figure 1 that apart from one early withdrawal on isoxicam, the remaining patients stayed on treatment. In contrast, patients dropped out of piroxicam

Table 3 Statistical analysis of outcome variables

	Baseline Isoxicam vs piroxicam	Visit 2 vs baseline isoxicam	Level 1 Visit 2 vs baseline piroxicam	Visit 2 Isoxicam vs piroxicam
Night pain	0.36	0.06	0.04*	0.99
Pain on walking	0.37	< 0.01*	0.07	0.02*
Standing pain	0.17	0.21	0.34	0.07
Pain on movement	> 0.05	0.05*	< 0.01*	0.16
Joint tenderness	0.09	0.06	< 0.01*	0.99
Joint swelling (knee)	0.21	0.32	0.36	0.16
Range of movement (knee)	0.52	0.22	0.43	0.10
Intermalleolar straddle (hips)	0.33	0.64	0.98	0.15
Analogue scale of pain	0.66	< 0.01*	0.02*	0.24
Overall assessment (MD)	0.65	< 0.01*	0.04*	0.21
Overall assessment (patient)	0.90	< 0.01*	0.07	0.28
Walking time	0.96	0.40	0.42	0.72

* $P \leq 0.05$

Table 4 Statistical analysis of outcome variables

	Baseline	Visit 4 vs baseline	Level 1 + 2 Visit 4 vs baseline	Visit 4 Isoxicam vs piroxicam
	Isoxicam vs piroxicam	isoxicam	piroxicam	
Night pain	0.36	< 0.01*	< 0.01*	0.51
Pain on walking	0.37	< 0.01*	< 0.01*	0.75
Standing pain	0.17	< 0.01*	< 0.01*	0.46
Pain on movement	> 0.05	< 0.01*	< 0.01*	0.49
Joint tenderness	0.09	< 0.01*	< 0.01*	0.91
Joint swelling (knee)	0.21	0.04*	0.10	0.13
Range of movement (knee)	0.52	0.14	0.14	0.20
Intermalleolar straddle (hips)	0.33	0.16	0.18	0.19
Analogue scale of pain	0.66	< 0.01*	< 0.01*	0.18
Overall assessment (MD)	0.65	< 0.01*	< 0.01*	0.66
Overall assessment (patient)	0.90	< 0.01*	< 0.01*	0.99
Walking time	0.96	0.24	0.07	0.84

* $P \leq 0.05$

therapy at intervals and as late as the thirty-eighth day of treatment.

An end-of-study comparison between the active treatment phase and the washout period, based on patient evaluations, indicated that 93% of isoxicam patients had improved vs 69% of piroxicam patients. Physician-based estimates for these same comparisons were 93% and 75% respectively. In the isoxicam group, 73% of

patients and 72% of physicians considered the study drug better than the patient's pre-study medication. In the piroxicam group, 61% of patients and 73% of physicians considered the study drug better than patient's pre-study medication. Eighty-nine percent of patients and 96% of physicians rated isoxicam to have been as well or better tolerated than the pre-study medication.

Table 5 Adverse reactions reported by the two treatment groups

Reactions	Isoxicam (n = 28)	Piroxicam (n = 29)	
Abdominal cramps	1	1	
Ankle swelling	1	5	
Asthenia	0	1	
Diarrhoea	0	1	
Dizziness	0	2	
Drowsiness	1	2	
Dry mouth	2	1	
Epigastric pain	0	2	
Hot flushes	1	1	
Metallic taste	1	1	
Nausea and vomiting	0	1	
Oral ulcer	0	1	
Nightmare	1	0	
Shortness of breath	1	3	
Skin rash	0	1	
Swollen ear,	0	1	
Difficulty swallowing			
Tinnitus	2	0	
Tingling of tongue	1	0	
Total number of adverse reactions (ADR) +	12	24	
Total number of patients experiencing ADR	6	12	$P = 0.105$
Total number of patients with severe ADR	0	5	$P = 0.03^*$
Total number of patients withdrawn due to ADR++	1	5	$P = 0.105$
Total number of patients withdrawn due to either inefficacy or ADR	1	6	$P = 0.056$

+ Some patients had more than one adverse reaction.

++ One patient withdrawn due to a moderate adverse reaction.

* $P \leq 0.05$

Figure 1 Log rank Chi square comparison of cumulative rates (for continuing treatment (▲ isoxicam, △ piroxicam). Note break in vertical scale.

Derangements of haematological and biochemical variables were infrequent and no extreme abnormalities were noted. The haemoglobin fell below the lower limit of the normal range in three isoxicam and three piroxicam treated patients. Elevation of the serum creatinine was observed in one isoxicam and two piroxicam treated patients, elevation of the SGOT in two piroxicam treated patients, and elevation of the alkaline phosphatase in two isoxicam patients.

Discussion

The elderly represent a subset of the general population in whom degenerative forms of arthritis are common, concurrent illness not infrequent, and multiple drug therapy is prevalent. The study of the elderly is particularly important since individuals in this age group are frequent recipients of drugs which have been evaluated largely in younger subjects. Thus, given the relative frequency of osteoarthritis and its tendency to affect the middle-aged and elderly, this trial provides important efficacy and tolerability data on isoxicam in this subset of the population with musculoskeletal-disease. Although the titration strategy for dose adjustment does not allow simple dose-by-dose comparison (because of the small residual sample sizes), it does nevertheless allow isoxicam and piroxicam to be compared under simulated practice conditions.

The results of this study can be generalized to similar elderly patients fulfilling the defined inclusion and exclusion criteria and those who are treated under the described titration strategy.

It is traditional in comparative studies of this type to exclude high-risk patients, particularly those with severe disease of any major organ system or prior gastrointestinal bleeding. Accordingly, the results of this clinical trial cannot necessarily be extrapolated to patients with serious concomitant disease.

The result of this study indicate that isoxicam is an efficacious non-steroidal anti-inflammatory agent which significantly reduces pain, swelling and joint tenderness in elderly patients with osteoarthritis. Although some patients demonstrate a response to 100 mg day⁻¹ of isoxicam, the majority require a dosage of 200 mg day⁻¹. The beneficial effects of isoxicam are in general similar to those of the drug piroxicam.

Three measures of physical function (knee range of movement, intermalleolar straddle, and 50 foot walking time) failed to improve on either agent. Two factors may explain this failure in response. First, since range of knee movement was analyzed only for patients in whom the knee was the most severely affected joint and intermalleolar straddle only analyzed for those in whom the hip was the most severely affected joint, the sample sizes employed in the analysis were small and therefore the statistical power was low. Second, both these measures are attended by significant inter-observer variation which may have reduced the chance of detecting a statistically significant improvement. Response failure on the 50-foot walking time was not entirely unexpected as this outcome measure has previously displayed poor performance characteristics in clinical trials in osteoarthritis (Bellamy & Buchanan, 1984). Since pain is often the limiting factor in degenerative forms of arthritis, it is not surprising that relief of pain might enhance the ease of performing a particular task without necessarily improving the speed at which it can be accomplished. Although it is purely speculative, this may provide an explanation for the poor performance of the 50-foot walking time. An alternate explanation is that the difference between a healthy and a diseased elderly patient with osteoarthritis in respect of the ability to perform the walking time is less than between a healthy young individual and a young arthritic patient and, therefore, the response potential is more restricted in the elderly.

It is important that a new non-steroidal anti-inflammatory agent for elderly patients be not only efficacious but also well tolerated. The discontinuation of only one isoxicam patient due to a moderate adverse reaction compared to five piroxicam patients suggests that, in general, isoxicam may be better tolerated by the elderly

than piroxicam. Although the life table approach is infrequently used in the analysis of drug trials it has the ability to discriminate between different patterns of withdrawal from treatment. Whilst between-group differences were not

statistically significant, nevertheless the ability of patients to stay on treatment with isoxicam was notable. These data suggest that isoxicam may be a useful drug in the treatment of osteoarthritis in the elderly.

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