DIFLUNISAL: SIX-MONTH EXPERIENCE IN OSTEOARTHRITIS

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- 1 The analgesic efficacy and tolerance of diflunisal in patients with osteoarthritis has been compared with ibuprofen and acetylsalicylic acid (ASA) in two clinical studies carried out double-blind for 12 weeks and then continued single-blind for a further 12 weeks. The studies involved 115 patients and 695 patients, respectively.
- 2 Diflunisal was superior to ibuprofen in overall response, as assessed by both patients and investigators ($P < 0.01$), improvement in disease activity and by improvement in internal rotation of the hip ($P < 0.05$).
- 3 Diflunisal was superior to ASA in overall response, as assessed by both patients and investigators, therapeutic index ($P < 0.01$), reduction in morning stiffness, and by improvement in performance of daily activities ($P < 0.05$).
- 4 In the first study, the mean daily dose of diflunisal during the double-blind period was 702 mg and of ibuprofen 1161 mg. In the second study, the mean daily dose of diflunisal was 612 mg and of ASA 2461 mg.
- 5 Diflunisal produced fewer gastrointestinal side-effects after 24 weeks of therapy than did ibuprofen ($P < 0.01$).
- 6 Diflunisal produced fewer general side-effects and fewer gastrointestinal side-effects during the double-blind and the single-blind phases of the study ($P < 0.01$). Fewer patients discontinued therapy because of side-effects in the diflunisal group than in the ASA group ($P < 0.05$).
- 7 Both ASA and diflunisal decreased serum uric acid, with diflunisal being more uricosuric than aspirin ($P < 0.01$).

Introduction

Diflunisal (2',4'-difluoro-4-hydroxy-3-biphenyl-carboxylic acid) has been shown to be an effective and well-tolerated analgesic in short-term use (Tempero *et al.*, 1977). Osteoarthritis provides a relatively stable and predictable clinical picture in which to measure the long-term efficacy and safety of an analgesic, since the main symptom is pain and its relief is the most important part of therapy (Haslock, 1976). The most recently introduced class of antiarthritic compounds are the propionic acid derivatives, and the first study described here used ibuprofen as the comparative agent. Ibuprofen has analgesic and mild anti-inflammatory activity, making it a suitable drug for the treatment of the less severe forms of osteoarthritis (Owen-Smith & Burry, 1972). The second study used acetylsalicylic acid (ASA), which is still a widely used analgesic in the treatment of osteoarthritis.

Methods

Two separate studies were carried out using several clinics in order to collect data on the comparative

efficacy and safety of diflunisal in osteoarthritis of the hip or knee. One study used ibuprofen as an active control; the other used ASA for this purpose. Both studies followed a double-blind, parallel design for 12 weeks. Patients were then continued in a single-blind, parallel format for an additional 12 weeks to provide 24-week patient experience. The clinical trials were carried out in accordance with the Declaration of Helsinki, and the protocols were approved by individual hospital ethical committees.

Clear definitions of the patient population to be studied and the clinical variables used to evaluate efficacy were provided. A definite diagnosis of active osteoarthritis required the presence of hip or knee pain, which was aggravated by motion and at least partially relieved by rest, limitation of passive motion and the presence of inactivity stiffness. In addition, at least grade 2 changes were to be present on X-ray examination. Patients with serious complicating diseases or other forms of arthritis were excluded. The concurrent administration of systemic steroidal or non-steroidal anti-inflammatory agents, barbiturates, ASA or other analgesic drugs was forbidden. Physical

therapy begun before the study could be continued unchanged, but no physical therapy was to be commenced at any time during the study.

Study 1 (diflunisal compared with ibuprofen)

In study 1 (ibuprofen comparison), 115 patients from four investigators had all antiarthritic therapy withdrawn for a maximum of 7 d and were then randomly allocated to either diflunisal or ibuprofen therapy. Each patient received both the assigned active drug and a placebo for the comparative drug because of the physical dissimilarities of the two therapies. Dosage began with diflunisal 500 mg daily (two 125 tablets morning and night) or ibuprofen 800 mg daily (two 200-mg capsules morning, one 200-mg capsule mid-day and at night). If response was less than desired, dosage was increased 1 week later to diflunisal 375 mg twice daily or ibuprofen 400 mg three times daily. At the end of 12 weeks, patients continued to receive their maintenance dosage of the active drug on a single-blind basis for an additional 12 weeks.

Study 2 (diflunisal compared with ASA)

In study 2 (ASA comparison), 695 patients from 41 investigators were entered into the study after a drug withdrawal period of up to 7 days. Patients were randomly assigned to receive diflunisal 250 mg twice daily or ASA 500 mg four times daily. To maintain the double-blind nature of the study, each patient received both capsule-shaped tablets (A) and round-shaped tablets (B). Tablet A contained either diflunisal 125 mg or ASA 250 mg. Tablet B contained either ASA 250 mg or placebo. Medication was taken on a four times daily dose regimen with the diflunisal group having active tablets for only two of the doses. Dosage could be increased after 1 week to diflunisal 750 mg daily or ASA 3000 mg daily. The investigators were advised not to increase dosage unless the clinical response to the initial dosage was unsatisfactory. At the end of the double-blind phase patients could be continued on their established dosage in a single-blind fashion for an additional 12 weeks.

Examination criteria

Patients were examined immediately before initial administration of the test drug to provide baseline values; each patient was subsequently examined at fixed intervals throughout the 24-week study.

The efficacy criteria involved evaluation of both subjective and objective variables. Pain on bearing weight, pain associated with both active and passive movement, and night pain were rated on a five-point scale with strictly defined categories ranging from absence of pain to pain that was totally disabling or seriously interfered with sleep. Inactivity/stiffness was measured as the time necessary to gain appreciable improvement after inactivity. To assess the patient's functional ability one activity of daily living that the osteoarthritis interfered with most was selected for each patient and rated on a five-point scale. Limitation of motion was measured (in degrees) for internal and external rotation of the hip and flexion of the hip and knee. Hip abduction was measured as the intermalleolar distance (cm). An overall assessment of therapeutic response was made by both the patient and the investigator using a five-point scale, and the investigators also assessed the degree of overall disease activity.

A comprehensive battery of laboratory tests was carried out to detect any possible effect on the renal, hepatic, or haematopoietic systems. In a proportion of the patients' ECGs, ophthalmological, and audiometric examinations were carried out after 12 and 24 weeks of therapy. Adverse effects were elicited from patients at each visit by discussing with him his general well-being and asking whether he had any complaints; the physician did not itemize specific side-effects by direct questioning. All adverse reactions were evaluated as to their nature, intensity, duration, their possible relationship to the test drug, action taken, and the outcome.

To provide an overall evaluation of the practical benefit of the test drug to the patient, a therapeutic index was constructed using the investigators' assessment of overall therapeutic response and his assessment of side-effects. The response of each patient could then be categorized as excellent (1), good (2–4), fair (5–7), or poor (> 7) as shown in Table 1.

Table 1 Therapeutic index

<i>Side-effect</i>	<i>Efficacy</i>		<i>Efficacy</i>		
	<i>Excellent</i>	<i>Good</i>	<i>Fair</i>	<i>Poor</i>	<i>None/Worse</i>
None	1	2	6	10	14
Mild	3	4	8	13	17
Moderate	5	7	12	15	18
Severe	9	11	16	19	20

Thus, the therapeutic index was considered excellent (or optimal) in those patients who had an excellent efficacy rating and no side-effects. The index was considered good in those patients with an excellent efficacy rating with mild side-effects or a good efficacy rating with no or mild side-effects. The fair therapeutic index represented patients with an excellent or good efficacy rating and moderate side-effects or patients with a fair efficacy rating and no side-effects. The test drug was therefore considered to have been effective and adequately tolerated in patients with an excellent, good or fair therapeutic index.

The statistical analysis of the results of the evaluations of the efficacy variables was based on a Kruskal-Wallis ranking procedure for between-group comparisons. In the assessment of the usefulness of an analgesic, it is necessary to include the patients who did not complete the study because of therapeutic inefficacy. Patients who dropped out of the study because of adverse reactions or lack of therapeutic effect were included in the analyses of the overall assessments of efficacy and were assigned an evaluation worse than all patients who remained in the study.

Results

Study 1

Of the 115 patients who entered the study, 13 were excluded from the efficacy analyses because of major protocol violations or irregularities in drug administration. During the double-blind period of the study, 11 discontinued therapy because of adverse reactions, lack of therapeutic effect, or loss to follow-up. Both groups were comparable at baseline with one

exception – that is, the proportion of patients having a flare on initial drug withdrawal was greater for the diflunisal group than the ibuprofen group.

At the end of week 12, both treatment groups showed statistically significant improvements from baseline for every efficacy variable measured. For the individual pain variables monitored, improvement was greater with diflunisal than with ibuprofen. The diflunisal group had a significantly greater improvement from pretreatment in pain caused by bearing weight, pain with active or passive movement, and night pain ($P < 0.05$ in each case).

The mean changes from pre-treatment for the objective variables are shown in Table 2. The hip patients treated with diflunisal had a greater improvement in internal rotation than the ibuprofen patients ($P < 0.05$). There were also trends favouring diflunisal in hip and knee flexion and in hip abduction, although these differences were not consistent enough to reach statistical significance at the $P = 0.05$ level.

The assessments of overall response by both the patients and the investigators showed a greater improvement in the diflunisal patients than in the ibuprofen patients. Tables 3 and 4 show the percentage of patients in each response category. According to the patients' assessments, 94% of the diflunisal group responded (better or much better than baseline) to treatment compared with 73% for ibuprofen. The investigators rated 87% of the diflunisal group as responders (excellent or good) compared with 54% for ibuprofen. In both instances the difference between diflunisal and ibuprofen was significant ($P < 0.01$). In addition, the investigators' assessment of improvement in disease activity showed a significantly greater improvement from pretreatment for the diflunisal group than the ibuprofen group ($P < 0.05$).

At the end of the single-blind extension period (24

Table 2 Pre-treatment and post-treatment mean values

	<i>Diflunisal</i>		<i>Ibuprofen</i>	
	<i>Baseline</i>	<i>Week 12</i>	<i>Baseline</i>	<i>Week 12</i>
Flexion deformity (hip) (degrees)	17.3	9.7	13.9	10.6
Flexion deformity (knee)	5.0	2.4	8.0	5.6
Flexion (hip)	85.0	100.9	90.0	98.3
Flexion (knee)	98.7	111.6	101.3	110.4
Inactivity stiffness (hip) (minutes)	58.6	13.0	62.6	18.3
Inactivity stiffness (knee)	33.2	8.5	35.3	16.8
Internal rotation (hip)* (degrees)	10.5	15.9	15.0	16.7
External rotation (hip)	12.3	20.0	18.3	23.3
Intermalleolar distance (cm)	56.0	64.6	54.0	58.2

* More improvement from pre-treatment for diflunisal than for ibuprofen ($P < 0.05$).

weeks), the results were essentially the same as those observed at the end of the 12-week double-blind period. Tables 5 and 6 show the percentage of patients in each overall response category. According to the patient assessments, 96% of the diflunisal group were much better or better than at pretreatment, compared with 74% for the ibuprofen group. The investigators rated 90% of the diflunisal group as having an excellent or good overall response compared with 60% of the ibuprofen group. These differences between the treatment groups were statistically significant ($P < 0.05$).

Drop-outs and side-effects One patient in the diflunisal group and two in the ibuprofen group withdrew from the study because of lack of therapeutic effect. In addition, two patients in the ibuprofen group discontinued therapy because of gastrointestinal distress. No patients discontinued diflunisal because of side-effects. The most common side-effect in both groups was gastrointestinal pain. Although the difference was not consistent enough to reach statistical significance, more patients in the ibuprofen group had digestive system side-effects than did patients in the diflunisal group during the double-blind period of the study. After 24 weeks of therapy, the proportion of ibuprofen patients with digestive system side-effects was significantly higher than the proportion of diflunisal patients with comparable complaints ($P < 0.01$). The number of patients

experiencing the most common side-effects are shown in Table 7.

The only consistent change in laboratory values was a decrease in the mean haemoglobin value in the ibuprofen group from 14.1 g per 100 ml at baseline to 13.8 g per 100 ml at week 12 and 13.6 g per 100 ml at week 24. The change from baseline at both times was statistically significant ($P < 0.05$).

Study 2

Of the 695 patients who entered this study, 14 were excluded from the efficacy analyses because of major protocol violations or irregularities in drug administration. During the double-blind period of the study, 176 patients discontinued therapy because of adverse reactions, or lack of therapeutic effect or loss to follow-up. Both groups were comparable at baseline.

At the end of week 12, both treatment groups showed statistically significant improvements from baseline in each efficacy variable with two exceptions. In the two pain variables, night pain and pain caused by bearing weight, there was no statistically significant difference between the two groups in improvement. The mean changes from pretreatment for the objective variables are shown in Table 8. Both treatments were equally effective in improving hip abduction and knee flexion. The patients treated with diflunisal, however, had a significantly better reduction in inactivity

Table 3 Patient assessment of overall response (Week 12)

	<i>Diflunisal</i>	<i>Ibuprofen</i>
Total number in analysis	52	41
Much better	31 (59.6)	12 (29.3)
Better	18 (34.6)	18 (43.9)
Unchanged	3 (5.8)	9 (22.0)
Worse	0 (0)	2 (4.9)
Much worse	0 (0)	0 (0)

Percentage of patients in parentheses.

Table 4 Investigators assessment of overall response (week 12)

	<i>Diflunisal</i>	<i>Ibuprofen</i>
Total number in analysis	53	41
Excellent	29 (54.7)	10 (24.4)
Good	17 (32.1)	13 (31.7)
Fair	7 (13.2)	12 (29.3)
Poor/None	0 (0)	6 (14.6)

Percentage of patients in parentheses.

Table 5 Patient assessment of overall response (week 24)

	<i>Diflunisal</i>	<i>Ibuprofen</i>
Total number in analysis	48	35
Much better	31 (64.6)	10 (28.5)
Better	15 (31.2)	16 (45.7)
Unchanged	2 (4.2)	7 (20.0)
Worse	0 (0)	1 (2.9)
Much worse	0 (0)	1 (2.9)

Percentage of patients in parentheses.

Table 6 Investigator assessment of overall response (week 24)

	<i>Diflunisal</i>	<i>Ibuprofen</i>
Total number in analysis	48	35
Excellent	27 (56.3)	9 (25.8)
Good	16 (33.3)	12 (34.3)
Fair	5 (10.4)	12 (34.3)
Poor/None	0 (0)	2 (5.6)

Percentage of patients in parentheses.

stiffness than the ASA group. In the other specific evaluation of general function improvement, namely performance of a specific function in the patients' normal daily activities, the diflunisal group showed a significantly greater improvement than the ASA group ($P < 0.05$).

The assessments of overall response to therapy by both the investigators and the patients showed a consistently greater improvement in the diflunisal group than in the ASA group ($P < 0.01$). The therapeutic index corroborated this conclusion, the diflunisal group responding to therapy better than the ASA group as also measured by this index. Table 9 shows the percentage of patients in each category.

Diflunisal was effective and adequately tolerated (excellent, good or fair) in 70% of the patients receiving it, compared with 58% of the patients receiving ASA. This difference is significant ($P < 0.01$). In addition, a greater proportion of patients did not continue on ASA therapy because of poor therapeutic response or adverse experiences.

At the end of the single-blind extension period, when patients had received a total of 24 weeks of therapy with ASA or diflunisal, the effects of each therapy were similar to those seen at the end of the double-blind period. The assessments of overall response after 24 weeks of therapy were consistently in favour of diflunisal (Table 10).

Table 7 Number of patients with side-effects

	Weeks 1–12		Weeks 13–24	
	Diflunisal	Ibuprofen	Diflunisal	Ibuprofen
Total number of patients	58	57	53	47
Number with side-effects	16 (27%)	22 (38%)	7 (13%)*	15 (31%)*
Digestive system	13 (22%)	20 (35%)	4 (7%)†	13 (28%)†
Dizziness	2	3	0	1
Headache	2	1	0	0

* Significant difference: $P < 0.05$.

† $P < 0.01$.

Table 8 Pre-treatment and post-treatment mean values

	Diflunisal		Ibuprofen	
	Baseline	Week 12	Baseline	Week 12
Flexion (knee) (degrees)	104.8	111.7	102.4	110.1
Intermalleolar distance (cm)	63.1	71.0	63.4	72.0
Inactivity stiffness* (min)	30.6	6.1	23.9	7.4

* More improvement from pre-treatment for diflunisal than for ASA ($P < 0.01$).

Table 9 Therapeutic index (week 12)

	Diflunisal		ASA	
	No of patients	%	No of patients	%
Excellent	60	20	38	12
Good	95	32	96	32
Fair	53	18	44	14
Poor	44	15	45	15
TRD Inefficacy	17	6	30	10
Adverse effects	30	10	50	17
Total number of patients	299		303	

TRD, Treatment-related drop-outs included in analysis.

Table 10 Overall assessments of response (week 24).

	<i>Diflunisal</i> *	<i>ASA</i> *	<i>Between-group difference</i>
Total number in analysis	99	91	
Therapeutic index (excellent, good, fair)	94	80	$P < 0.05$
Investigators' assessments (excellent, good)	75	61	$P < 0.05$
Patients' assessments (excellent, good)	76	62	$P < 0.05$

* Percentage of patients.

Table 11 Number of patients with side-effects

	<i>Weeks 1–12</i>		<i>Weeks 13–24</i>	
	<i>Diflunisal</i>	<i>ASA</i>	<i>Diflunisal</i>	<i>ASA</i>
Total number of patients	345	350	139	123
Number with side-effects	124 (36)†	171 (49)†	18 (13)†	36 (29)†
Digestive system	87 (25)†	143 (40)†	10 (7)†	30 (24)†
Dizziness/Vertigo	8 (2)	13 (4)	2	1
Headache	9 (3)	7 (2)	1	0
Tinnitus	1	7*	0	1
Other	56	58	8	7

Difference in proportion between the treatment groups: * $P < 0.05$; † $P < 0.01$, respectively.

Note that a patient may have had more than one side-effect.

§ Percentage of patients in parentheses.

Table 12 Laboratory mean values

	<i>Diflunisal</i>		<i>ASA</i>	
	<i>Week 0*</i>	<i>Week 12</i>	<i>Week 0</i>	<i>Week 12</i>
Haemoglobin value (g per 100 ml)	13.9	14.3**	14.1	14.1
Haematocrit value (%)	42.4	43.2**	42.6	42.2
Uric acid (mg per 100 ml)	6.5	5.5**	6.1	6.0
	<i>Week 0†</i>	<i>Week 24</i>	<i>Week 0</i>	<i>Week 24</i>
Haemoglobin value (g per 100 ml)	14.1	14.2	14.3	13.5**
Haematocrit value (%)	42.9	43.5§	42.8	43.0
Uric acid (mg per 100 ml)	6.6	5.2**	5.2	5.3

* Baseline for those patients completing week 12.

† Baseline for those patients completing week 24.

§ Significant change from baseline: $P < 0.05$.** Significant change from baseline: $P < 0.01$.

Drop-outs and side-effects During the 12-week double-blind period of the study, 17 patients discontinued diflunisal therapy for lack of effectiveness, compared with 30 patients treated with ASA. This difference is statistically significant ($P < 0.05$). Side-effects caused 30 diflunisal patients to discontinue therapy compared with 50 in the ASA group. This distinction between the two groups is also statistically significant ($P < 0.05$). One patient in each group had a cerebrovascular accident, and one patient developed severe gastrointestinal pain after 2 d of ASA therapy; this individual was subsequently treated for gastric ulcer. A hypersensitivity reaction with breathlessness, sweating, headache and elevated blood pressure occurred in one patient in the diflunisal group. After rechallenge testing, this was considered to be a reaction to a constituent of the placebo tablet.

The most common side-effects in both treatment groups were related to the digestive system, but incidence of these reactions was consistently lower in the diflunisal group than in the aspirin group ($P < 0.01$, see Table 11). In the investigators' assessment of the severity of side-effects, diflunisal was rated consistently as being associated with less severe reactions.

Several laboratory values were associated with statistically significant changes from baseline at various times during the study. Consistent changes and between-group differences were observed in haemoglobin and haematocrit values, and in serum uric acid levels (Table 12).

Ophthalmological, audiometric and ECG examinations carried out during and at the end of study, showed no clinically important changes attributable to either test drug.

Discussion

Pain, generally the main complaint of the patient with osteoarthritis, is a subjective response, and the patients' own assessments of its relief has been shown to be a sensitive parameter in the evaluation of antirheumatic drugs (Deodhar *et al.*, 1973). Compared with ibuprofen, diflunisal showed a greater relief of night pain, pain on active and passive movement, and pain caused by bearing weight. It is not surprising, therefore, that the patients' global assessments of their response to the test drug was significantly better for diflunisal than for ibuprofen. The investigators' evaluations agreed well with the patients' assessments. In a second study, the global evaluations of the patients and the investigators consistently found diflunisal superior to ASA, whereas night pain and pain caused by bearing weight were similar for the two therapies.

In the treatment of osteoarthritis the benefit/risk ratio is important (Rosenkrans *et al.*, 1976), and using both therapeutic effect and adverse clinical effects as a therapeutic index, diflunisal had a greater benefit/risk

ratio than ASA. Significantly fewer patients discontinued diflunisal therapy than ASA therapy due to poor therapeutic response, and, in addition, fewer discontinued therapy because of side-effects.

Gastrointestinal side-effects are associated with many forms of antiarthritic therapy. In these studies, diflunisal produced significantly fewer and less severe digestive system side-effects than ASA throughout 6 months of therapy. Diflunisal was also associated with a lower incidence of digestive system side-effects than ibuprofen.

Tinnitus was observed in a proportion of patients treated with ASA but only one case was reported with diflunisal at the dosages used.

Diflunisal therapy was not associated with any adverse effect on the haematopoietic system. Haemoglobin and haematocrit values were maintained at or above baseline values in the diflunisal group, but in both studies the active control drug (ASA or ibuprofen) showed decreases in the haemoglobin value after 6 months. Short-term studies have also demonstrated a fall in haemoglobin with ibuprofen (Mena *et al.*, 1976), and a decrease in the haemoglobin value has also been considered one of the hazards of ASA treatment (Rosekrans *et al.*, 1976). The clinical importance of diflunisal's lack of effect on haemoglobin levels is not clear, since a recent study showed no appreciable change in peripheral blood values during long-term treatment with ibuprofen or ASA, with no correlation between haemoglobin values and tendency for gastrointestinal bleeding (Schmid & Culic, 1976). A uricosuric effect has already been reported in short-term studies with diflunisal (Tempero *et al.*, 1977), and in the present study, a significant uricosuric effect was present for 6 months.

These two studies provide over 47,000 patient-days of experience with diflunisal, and demonstrate its efficacy and safety in the clinical management of pain associated with osteoarthritis. Diflunisal is a worthwhile and superior addition to available analgesics.

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