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Comparison of Aceclofenac with Piroxicam in the Treatment of Osteoarthritis

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Summary **A multicentre, double-blind, randomised, parallel group study was undertaken to investigate the efficacy and safety of aceclofenac (123 patients, 100 mg twice daily) in comparison to piroxicam (117 patients, 20 mg once daily and placebo once daily) in patients with osteoarthritis of the knee. The treatment period of two months was preceded by a washout period of one week duration. On completion of the study, patients in both aceclofenac and piroxicam-treated groups exhibited significant improvement in pain intensity and functional capacity of the affected knee, as represented by the Osteoarthritis Severity Index (OSI) ($p < 0.0001$ and $p < 0.001$ respectively). This was further substantiated following the patient's assessment of pain intensity using the Visual Analogue Scale (VAS), in which significant improvements were demonstrated at all time points for each treatment group ($p < 0.001$). Although both treatment groups showed a significant improvement in all investigator's clinical assessments (functional exploration of the knee, knee flexion and extension (EXT)), there were no significant differences between the groups. There was, however, a more rapid improvement in knee flexion in the aceclofenac group after 15 days of treatment. Both aceclofenac and piroxicam were well tolerated by patients, the most commonly reported adverse events being gastrointestinal, although their incidence was low. Only 24 patients on aceclofenac, as opposed to 33 on piroxicam complained of dyspepsia, epigastralgia and pyrosis. While 7 patients in each group were withdrawn because of adverse events, only one patient with piroxicam was withdrawn because of severe upper gastrointestinal bleeding. Twice as many reports of fecal blood loss were made in the piroxicam group in comparison to the aceclofenac group. In summary, this study confirms the therapeutic efficacy of aceclofenac and suggests that it is a well-tolerated alternative NSAID to piroxicam in the treatment of osteoarthritis.**

Key words **Aceclofenac, NSAID, Piroxicam, Osteoarthritis, Efficacy, Safety**

INTRODUCTION

Osteoarthritis (OA) is a frequent cause of pain and disability in joints (1) and uniformly accompanies ageing. The natural cause of this chronic condition is not well understood (2). Generally, it has an insidious onset and a variable relationship of symptoms and functional impairment with slowly evolving pathologic and radiographic changes. The disease may or may not be associated with inflammation (3).

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Nonsteroidal anti-inflammatory drugs (NSAIDS) have long been the preferred therapy for relief of the pain and stiffness of arthritic diseases, including OA, because of their analgesic and anti-inflammatory properties, although their use in this condition has sparked controversy (4). In terms of pain relief, a recent study found that 75% of patients ranked the NSAIDs as good or excellent as did 45% of the physicians (5). An indication of the efficacy of these drugs is the high number of prescriptions written annually. In 1986, over 100 million prescriptions (4.5%) for NSAIDs (excluding aspirin) were dispensed in the USA (6), where the most common indication for use comprised arthritic pain syndromes and osteoarthritis. Despite their efficacy, the threat of serious adverse effects poses a major concern for chronic NSAID users. Adverse renal effects (7) and effects on bone and cartilage metabolism (8) are counted among worrisome NSAID-induced side effects, but serious gastro-intestinal complications represent the greatest threat to long-term NSAID therapy (9). Nevertheless numerous clinical trials have demonstrated the efficacy of NSAIDs in pain relief in OA patients (10, 11).

Aceclofenac, a novel NSAID, has recently been described as exhibiting good anti-inflammatory and analgesic efficacy in animal experimental models while maintaining better gastric tolerance as compared to other NSAIDS, such as indomethacin and diclofenac (12). Indeed the therapeutic index for aceclofenac was reported to be four times greater than that of diclofenac, which has been shown to be well tolerated in clinical use (13).

Short term clinical studies have demonstrated the efficacy of aceclofenac in pain relief following dental extraction and episiotomy (14,15), and in the chronic treatment of rheumatoid arthritis (16) and osteoarthritis (17, 18). In some comparative studies, there was a tendency for aceclofenac to be better tolerated than diclofenac (17, 19), with fewer patients being withdrawn from treatment due to gastric intolerance.

This paper describes a short term, double-blind, parallel group evaluation of the safety and efficacy of aceclofenac compared to an established NSAID (piroxicam) in patients with OA of the knee.

PATIENTS AND METHODS

Patients and study design

A double-blind, randomised, comparative, parallel group study was undertaken in 12 centres throughout Spain to investigate the efficacy and safety of aceclofenac (100 mg bd) in comparison with piroxicam (20 mg once daily) in patients with osteoarthritis of the knee joint. The treatment period was preceded by a washout period of a minimum of one week duration. The duration of treatment was 2 months, with control visits at selection, on randomization to treatment, at 15 days, 1 month and 2 months.

Patients of either sex (age 40-80 years) with confirmed radiologic and symptomatic OA of the knee were considered eligible for the study. OA was diagnosed on combined radiological (20) and clinical grounds which fulfilled all criteria established by the World Health Organisation (WHO) for the diagnosis of OA. Based on these diagnoses, active disease was defined by the following criteria: limitation due to pain on movement and/or tenderness at the extremes of knee extension and flexion; narrowing of the medial femurotibial space in standing position; osteophytis and/or subchondral osteocondensation and/or cyst. Eligible patients had to have a pain score of at least 4 cm on the Visual Analogue Scale (scale of 0-10 cm).

The exclusion criteria for the trial included: history of renal, hepatic, cardiovascular or connective tissue disease, diabetes or recent gastrointestinal or haematological disease, clinically significant non-OA arthropathies; a life-expectancy of < 2 years; recent haemorrhage or alcohol or drug abuse; recent febrile viral infection or major surgery; treatment with anti-coagulant or oral hypoglycaemic drugs or other drug which could interfere with the test medication; previous hypersensitivity or other reaction to any NSAID treatment with an investigational drug; intra-articular or parenteral steroids in the previous 2 months; pregnant or nursing females; women of child-bearing age not using adequate contraception.

Individual ethical committee approval was obtained from all participating hospital clinical trials committees and from the Minister of Health in Spain. The study followed the principles of Good Clinical Practice and was conducted in accordance with the declaration of Helsinki and Tokyo Guidelines for Ethics in Research, as well as the Spanish legislation on clinical trials. Written informed consent was obtained from all eligible patients prior to entry.

Based on previous comparative studies of aceclofenac with NSAIDs, a sample size of 111 patients per treatment group was considered sufficient to detect a difference between groups in the Osteoarthritis Severity Index of 21% at the 5% significance level with a power of 90%. Allowing for a 20% drop-out rate during the trial, a sample size of 139 per treatment group was considered appropriate.

Medication

Subjects who fulfilled the preliminary inclusion criteria, were instructed to stop NSAID medication for the washout period of at least one week. Paracetamol was issued as escape analgesia during the washout period.

A total of 240 patients, who satisfied all selection criteria, were randomly assigned to receive either aceclofenac 100mg twice-daily (bd) (n=123), or piroxicam 20mg once, in the evening and a placebo tablet in the morning to maintain double-blind conditions (n=117) for 2 months. No other analgesics or anti-inflammatory agents were permitted during the trial.

Efficacy and safety variables

The initial screening assessment consisted of a full medical history including both radiological and clinical verification of the disease. Blood and urine samples were taken for routine laboratory screens which included full blood count, plasma proteins, renal and hepatic function tests. In addition faecal samples were obtained to detect blood loss.

Clinical efficacy assessments were undertaken on inclusion into the study and were repeated 15 days following commencement of treatment and at one and two months thereafter. Faecal blood loss was also monitored using Hemolex reactive strips (based on detection with anti-Hb antibodies) at all visits. Laboratory safety parameters were repeated at the final evaluation (2 months).

The following clinical efficacy assessments were made:

- The Lequesne Osteoarthritis Severity Index (OSI) (21, 22), consisting of total scores for a series of questions assessing nocturnal pain, pain on movement and duration of morning stiffness or pain on rising (all scored 0-2; 0 = absent), pain on standing for 30 min (0 = no; 1 = yes), maximal walking distance (scored 0-6; 0 = 1 km without limitation, 6 = less than 100m, +1 for use of stick, +2 for use of two crutches) and daily activities (5 activities each scored 0-2, where 0 = no difficulty). The index value was calculated for each knee joint by adding all scores and the most painful joint was used for each patient. Only patients with an OSI between 5 and 17 were eligible for the study.
- Knee function, calculated by adding the individual scores (from 0 to 3, 0 = absent) for pain on movement, pain on pressure, spontaneous pain, crepitation, muscular atrophy and swelling (21).
- Flexion and extension capacity of the knee measured using a goniometer and recorded in degrees.
- Pain measured on a Visual Analogue Scale (0 cm - 10 cm, 0 cm = no pain) (23).

The nature of any adverse events was recorded at each visit, and a count of returned tablets made to check compliance. Furthermore, when any patient withdrew prematurely from the study a note was made of the time at which trial medication was stopped, and the reason for withdrawal.

Statistical analysis

The statistical significance of observed intra and intergroup modifications was calculated by the application of non-parametric tests for baseline categorical variables (Chi squared) and by Student's t-test on a completer basis for continuous variables (paired in the intra-group comparison and unpaired in the intergroup comparisons). The possible relationships between the different observed variables and the modifications obtained were analysed using correlation and linear regression coefficients, as appropriate. In all statistical tests, the probability of type I error was set at 0.05, 2-tailed. Data were analysed using SPSS/PC +4.0 software (Statistical Program for Social Sciences, Chicago, IL, USA).

RESULTS

Patient characteristics

Two hundred and forty patients (all Caucasians) were randomised and received treatment. One hundred and twenty three subjects received aceclofenac 100mg bd and 117 received piroxicam 20mg once daily in the evening and a morning placebo. The demographic parameters (Table I) were comparable in each group. Mean systolic and diastolic blood pressures were higher in the aceclofenac than in the piroxicam group. Two of the patients in the piroxicam group exhibited fecal blood loss at baseline, but all other laboratory parameters were within normal ranges.

Table I: *Demographic characteristics*

	Aceclofenac (n=123)	Piroxicam (n=117)
Male: Female	10 : 113	11 : 106
Age[a] (yrs.)	59.3±8.9	59.7±7.4
Weight[a] (kg)	78.2±12.4	77.2+12.5
Height[a] (cm)	156.2±6.4	157.4±7.5
Quetelet index[a] (kg/m^2)	32.2±5.5	31.2±4.9
Systolic BP[a] (mmHg)	145.4±18.4**	139.0±19.6
Diastolic BP[a] (mmHg)	84.1±10.4*	81.4±10.7
HR[a] (beats/min)	77.7±9.3	79.2±9.6

[a]Values are means ± SD
*$p<0.05$; **$p<0.01$ vs piroxicam

On completion of the study, 23 patients were found not to have complied with all the inclusion criteria, in spite of having partially or completely finished the study, and consequently were only included for analysis of tolerability. The remaining 217 subjects (109 on aceclofenac and 108 on piroxicam), were included for the analysis of efficacy, 103 patients in the aceclofenac group and 99 patients in the piroxicam group who completed the study as planned.

Efficacy

A total of 217 patients (109 on aceclofenac and 108 on piroxicam) were included in the efficacy analyses. Both treatment groups showed a statistically significant downward trend in the OSI from baseline, at each visit ($p < 0.0001$ and $p < 0.001$ for aceclofenac and piroxicam treated groups, respectively), as shown in Table II. However, there were no statistically significant differences between groups in the change in the OSI from baseline, at any visit or at endpoint ($p=0.48$). In addition, the patient's assessment of pain intensity, as measured using the Visual Analogue Scale (VAS), revealed significant improvements at all time points for each of the treatment groups ($p < 0.001$). There were no statistical differences between groups throughout the study or at end point ($p= 0.865$).

There were significant improvements in knee function at all visits for each of the treatment groups. However, no significant differences were revealed between treatment groups at any time point or at end point ($p= 0.787$), except at baseline when a significant difference was noted ($p= 0.01$) (Table II). The same was also true for knee flexion measurements which increased 11.48° from baseline to end point in the aceclofenac group and 8.46° in the piroxicam group ($p=0.376$). It is worth noting that significant improvements in flexion were seen at all time points in the aceclofenac group ($p < 0.001$). However, although a progressive improvement in knee flexion was evident in the piroxicam-treated group, the values failed to reach significance until one month of treatment. Significant improvements were also seen in knee extension at each visit and at end point for each of the treatment groups ($p < 0.001$). However, there were no statistical differences between the treatment groups at any time point throughout the study.

Safety and adverse events

A total of 240 patients (123 in the aceclofenac group and 117 in the piroxicam group) were included in the safety and tolerability assessments. Table III summarises the causes for withdrawal or discontinuation of treatment. One patient in the aceclofenac group and 3 patients in the piroxicam group discontinued treatment because of inefficacy. Seven patients in each group withdrew due to major adverse events. There was no comparative difference for discontinuation of treatment between groups ($p= 0.588$).

Table II: *The effects of aceclofenac and piroxicam on clinical efficacy variables*

Variables	Aceclofenac (n=109)		Piroxicam (n=108)	
Osteoarthritis Index[a]				
Baseline	12.10 ± 2.91	(109)	12.14 ± 2.94	(108)
15 days	8.92 ± 3.74b	(107)	9.15 ± 3.48b	(105)
1 month	8.19 ± 3.87b	(100)	8.47 ± 4.02b	(99)
2 months	7.54 ± 3.87b	(94)	7.15 ± 3.67b	(92)
Pain by VAS[a] (mm)				
Baseline	70.21 ± 15.90	(109)	71.81 ± 14.76	(108)
15 days	48.97 ± 21.48b	(107)	52.33 ± 21.99b	(105)
1 month	42.24 ± 24.90b	(100)	45.46 ± 24.41b	(99)
2 months	36.39 ± 23.46b	(94)	37.01 ± 25.84b	(91)
Knee function[a]				
Baseline	7.69 ± 3.05	(108)	6.64 ± 2.94e	(108)
15 days	5.08 ± 2.84b	(106)	5.01 ± 2.67b	(105)
1 month	4.42 ± 2.66b	(100)	4.25 ± 2.69b	(99)
2 months	3.96 ± 2.37b	(94)	3.86 + 2.60b	(92)
Knee flexion[a] (degrees)				
Baseline	116.44 ± 21.87	(108)	117.93 ± 22.00	(107)
15 days	122.02 ± 23.20b	(106)	120.34 ± 24.23	(105)
1 month	124.81 ± 22.11b	(100)	122.12 ± 24.35b	(99)
2 months	128.86 ± 20.84b	(94)	125.99 ± 23.41b	(92)
Knee extension[a] (degrees)				
Baseline	4.47 ± 6.67	(108)	4.51 ± 7.66	(106)
15 days	3.23 ± 4.87c	(106)	3.30 ± 5.87d	(105)
1 month	2.66 ± 4.52b	(100)	2.98 ± 6.11c	(99)
2 months	1.99 ± 3.76b	(94)	2.84 ± 5.09c	(92)

[a] Values are mean ± SD with no. of subjects in brackets
$b_p < 0.001$ vs. baseline
$c_p < 0.005$ vs. baseline
$d_p < 0.01$ vs. baseline
$e_p < 0.01$ vs. aceclofenac

Table III: *Causes for withdrawal or discontinuation of treatment*

	Aceclofenac	Piroxicam
End of treatment	103	99
Inefficacy	1	3
Adverse events	7	7
Concurrent complaints	1	1
Patient's decision	3	3
Loss of follow-up	7	4
Neoplasia by biopsy	0	0
Death	0	0
Other	1	0

Table IV: *Number of patients with adverse events*

Adverse events	Aceclofenac	Piroxicam
Dyspepsia, epigastralgia and pyrosis not leading to withdrawal:		
15 days	12	11
1 month	7	13
2 months	5	9
total	24	33
Requiring withdrawal:		
Gastrointestinal intolerance	5	3
Diarrhoea and abdominal pain	1	–
Haemorrhage of upper digestive tract	–	1
Headache and general upset	–	1
Alopecia pruritus	1	–
Oedema, pruritus and facial rubor	–	1
Haematomas in lower limbs	–	1
Total	7	7
Fecal blood loss[a]:		
pretreatment	–	2
15 days	2	1
1 month	–	3
2 months	2	4
total[b]	4	10

[a] Includes patients with upper GI haemorrhage
[b] Each report represents a different patient

Special attention was given to any gastrointestinal symptoms, and disorders of hepatic and renal function (Table IV). Five patients in the aceclofenac group and four in the piroxicam group withdrew from the study due to gastrointestinal intolerance. Another aceclofenac-treated patient discontinued treatment after an attack of diarrhoea and general abdominal pain. During active treatment, a further total of 24 gastrointestinal complaints were reported by the aceclofenac group, whereas 33 gastrointestinal complaints were reported in the piroxicam-treated group. These events included cases of dyspepsia, epigastralgias and pyrosis, which did not warrant discontinuation of medication as the complaints responded well to symptomatic treatment. Faecal blood loss was detected in 4 of the aceclofenac patients at different stages of the study. Two piroxicam-treated patients exhibited faecal blood loss at baseline. A further 8 reports of faecal blood loss were made in the piroxicam group throughout the study, which in one case (patient withdrawn due to gastric intolerance) was accompanied by severe blood loss due to a haemorrhage of the upper digestive tract.

No abnormal variations were detected in the analyses of hepatic enzymes and renal function in either treatment group throughout the trial. One patient in each group exhibited a transient increase in transaminase activity after 2 months which remained within the normal range.

Other major adverse events were reported for 1 patient in the aceclofenac group and 3 in the piroxicam group during the treatment period; 1 in the aceclofenac and 2 in the piroxicam group were considered to be drug-related. These included alopecia and pruritus in the aceclofenac group (which improved on discontinuing treatment), and headache, oedema, pruritus and facial and eyelid erythema in the piroxicam group. One patient treated with piroxicam presented with haematomas in both lower limbs and although this was not considered related to treatment, the subject was withdrawn from further treatment.

DISCUSSION

NSAIDs are widely prescribed to reduce joint pain and stiffness in OA, because of their analgesic and anti-inflammatory properties. Piroxicam is internationally well-established as a symptomatic therapy for OA and is similar in efficacy to other NSAIDS. The results of the present comparative study in OA, confirm the efficacy of aceclofenac and piroxicam, showing that significant improvements in all efficacy variables are obtained with both treatments. However, no significant differences were seen between aceclofenac and piroxicam groups. Throughout active treatment, the improvements in the indices of pain (OSI, VAS) and functional ability of the affected knee joint (OSI, knee function) were statistically significant for both treatment groups.

Both aceclofenac and piroxicam resulted in continuous and progressive improvement in knee extension and flexion at all time points. However, the time course of the improvement in knee flexion indicates that the onset of aceclofenac action was more rapid than that of piroxicam. The rapid effect of aceclofenac on knee flexion in OA has been observed in a previous study in which aceclofenac was found to act significantly earlier than diclofenac, possibly due to more rapid accumulation in the joint (19). In the present study, the earlier onset of action than piroxicam may have been related to the differences in dosing regimens.

A major problem exists with regard to the tolerance of NSAID therapy by the gastrointestinal tract in particular, and also the kidney and skin. Recent epidemiological studies on the risk of upper gastrointestinal bleeding with NSAIDs, indicate a moderate to high risk with piroxicam (23-25). This would appear to be confirmed in our study by the fact that 1 patient treated with piroxicam had severe upper gastrointestinal bleeding and a further 7/117 patients exhibited fecal blood loss during treatment. In contrast, only 4/123 patients in the aceclofenac group exhibited minor fecal blood loss. Although the number of patients withdrawing because of

gastrointestinal intolerance did not differ between the two treatments, a considerably smaller number of minor reports of gastrointestinal disturbances were reported in the aceclofenac than in the piroxicam group. Clearly, aceclofenac is associated with less severe adverse gastrointestinal events than piroxicam. In addition, no abnormal variations were detected in either renal function or hepatic enzyme analyses. Previous clinical studies on aceclofenac in OA (17-19) suggest that aceclofenac is not only efficacious as an analgesic in OA but is also better tolerated than several other NSAIDs.

In summary, the results of this study confirm the therapeutic potential of aceclofenac in degenerative joint disease and suggest that it is a well-tolerated alternative NSAID to piroxicam in the treatment of osteoarthritis.

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