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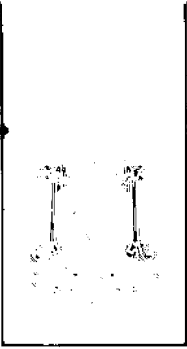
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REFERENCIA : SOLICITUD DE REGISTRO DE LA PATENTE
DENOMINADA **COMPOSICIÓN FARMACÉUTICA
QUE COMPRENDE CICLOBENZAPRINA Y
ACECLOFENAC EN ASOCIACIÓN** EXPEDIENTE
No. 08-129871
CODIGO : 01 - 01 - 08

JUAN CARLOS URIBE RESTREPO, mayor de edad, domiciliada en la ciudad de Bogotá D.C, República de Colombia, abogado titulado e identificado como aparece al pie de mi firma, en mi calidad de apoderado de la sociedad **INCREMENTHA P.D & I PESQUISA, DESENVOLVIMIENTO E INOVACÃO DE FARMACOS E MEDICAMENTOS LTDA**, existente y organizada conforme a las leyes del Brasil, con domicilio en la ciudad de Sao Paulo, Brasil, por medio del presente escrito doy respuesta a su oficio No. 11784, notificado por fijación en lista el 4 de julio de 2012, manifestando lo siguiente:

1. De conformidad con el artículo 46 de la Decisión 486 de la Comunidad Andina, el Despacho solicitó suministrar algunos documentos, en razón a que no le fue posible encontrarlos.
2. Teniendo en cuenta lo anterior, me permito adjuntar los siguientes:
 - 2.1 **BORENSTEIN D G** et al; Cyclobenzaprine and naproxen alone in the treatment of acute low back pain and muscle spasm; Clinical Therapeutics, Excerpta Medica; Princeton, NJ, US; Vol. 12, N°2 (1);pgs. 125-131
 - 2.2 **LEGRAND**; Expert Opin. Pharmacother., 5(6), pgs. 1347 – 1357 (2004).
 - 2.3 **KOBERLE G**, et al., Multicenter open study of the use of aceclofenac 100mg, twice a day, in the treatment of muscular-skeletal traumas. Vol 55, No. 1-2, 1998, pgs. 63-69.
 - 2.4 **EL-GHOBAREY A. F.** et al., Study of the efficacy and tolerability of bistaflam (aceclofenac) in the treatment of inflammatory and/or painful processes of musculoskeletal and joint diseases. Journal of Clinical Research, 1999, Vol. 2 N°155-163, pgs 155 -163.

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Los documentos en mención se aportan dentro del término concedido y en su versión original. Para mejor referencia del examinador, procederé a traducir los mismos con el fin de presentarlos a la mayor brevedad.

3. De conformidad con lo expuesto y habiendo cumplido con el requerimiento del Despacho, solicito al mismo continuar con el trámite de registro de la patente de la referencia.

De la Señora Jefe,

JUAN CARLOS URIBE RESTREPO
C.C. No. 79.159.313 de Usaquén
T.P.A. 54.493 del C. S. de la J.

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Cyclobenzaprine and Naproxen versus Naproxen Alone in the Treatment of Acute Low Back Pain and Muscle Spasm

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ABSTRACT

Two groups of 20 patients each, with mild to moderate acute low back pain with associated muscle spasm of ten days' duration or less, were treated with a combination of cyclobenzaprine and naproxen or naproxen alone in a randomized, 14-day open-label trial. Cyclobenzaprine was added to the naproxen regimen as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful, musculoskeletal conditions. The clinical characteristics of each study group, including the number of worker's compensation patients, were comparable. Combination therapy was associated with less objective muscle spasm and tenderness and greater motion of the lumbosacral spine ($P < 0.05$). There were trends toward faster resolution of functional deficits and pain with combined therapy. Combination therapy was associated with more side effects, due primarily to drowsiness from the cyclobenzaprine. The results of this study demonstrated that patients with

muscle spasm associated with acute low back strain benefited from the use of combination therapy consisting of a nonsteroidal anti-inflammatory agent (naproxen) and a muscle relaxant (cyclobenzaprine).

INTRODUCTION

Acute low back pain associated with muscle spasm is a common disorder. Treatment has included controlled physical activity, physical therapy, analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs).¹ Although muscle relaxants have been incorporated into the drug regimen, few studies^{2,3} have investigated the role of these agents in the management of patients with acute or chronic low back pain. In a double-blind multicenter trial, Basmajian⁴ reported that the combination of diflunisal and cyclobenzaprine was superior to single-drug therapy and placebo on the fourth day of a ten-day course of treatment for patients with acute back pain and muscle spasm.

To further document the utility of adding a muscle relaxant to an NSAID in the management of acute low back pain with muscle spasm, we conducted a prospective, randomized, open-label study comparing naproxen plus cyclobenzaprine to naproxen alone.

PATIENTS AND METHODS

Male and female patients between the ages of 18 and 60 years, with acute muscle spasm associated with mild to moderate back pain of ten days' duration or less, were eligible for entry into the study. Patients with work-related low back injuries were eligible.

Patients were excluded for any of the following reasons: initial pain characterized as severe; hypersensitivity to the study drugs; history of peptic ulceration; history of bleeding disorders, significant hypertension, or renal or hepatic disease; arrhythmia, heart block, congestive heart failure, or recent myocardial infarction; hyperthyroidism; marked obesity; neurologic symptoms, including sciatica; fracture; herniated intervertebral disk; intra-abdominal or pelvic conditions associated with referred low back pain; tumors or infections of the meninges or spinal cord; metabolic or toxic neuropathies; history of lumbosacral surgery; severe concurrent illness; treatment with anticoagulants, diuretics, corticosteroids, hydantoin, sulfonamides, sulfonylurea, lithium, probenecid, methotrexate, monoamine oxidase inhibitors, central nervous system depressants, anticholinergic drugs, other muscle relaxants, NSAIDs, or narcotic drugs; lactation or pregnancy; any mental or emotional disorders; or chronic low back pain.

Eligible patients were entered into the study if they agreed to follow the study

protocol and to sign the informed consent form. The study was approved by the Institutional Review Board of the George Washington University Medical Center.

Study Design

Patients who had low back muscle strain of short duration were referred to an orthopedist (Dr. Wiesel) or rheumatologist (Dr. Borenstein) by physicians at the George Washington University Medical Center. Patients were randomly assigned to one of two study groups before evaluation. A medical history was taken and physical examination performed to determine eligibility for the study.

Eligible patients were instructed on the appropriate use of the study drugs. Initially, 500 mg of naproxen* was given, followed by 250 mg every six hours thereafter; 10 mg of cyclobenzaprine† was given every eight hours to patients randomized to combination therapy. Patients kept a log of the times at which they took the study medications. They were informed about common side effects of the medications (eg, gastrointestinal effects with naproxen and drowsiness with cyclobenzaprine). They also were told not to take any additional medications and to limit their physical activity for three days, subsequently increasing activity as tolerated. Warm showers or baths twice daily were permitted.

Data on functional capacity and the degree of muscle spasm and tenderness were collected during the physical examination at the initial evaluation and three

*Trademark: Naprosyn® (Syntex Laboratories, Inc, Palo Alto, California).

†Trademark: Flexeril® (Merck Sharp & Dohme, West Point, Pennsylvania).

follow-up visits on days 3, 7, and 14. In addition, the degrees of range of motion of the lumbosacral spine, straight-leg raising test, Schober's test, and the degree of difficulty in arising from a supine position were assessed. Radiographic studies and laboratory tests were performed if a diagnosis other than acute muscle strain of the lumbosacral spine was suspected.

The degree of muscle spasm was rated on a four-point scale (0 = none; 1 = mild, with subjective complaint of tightness without objective evidence of muscle spasm; 2 = moderate, with loss of reversal of lumbar lordosis with flexion and paravertebral firmness; and 3 = severe, with loss of lordosis associated with abnormal gait). The spasm score was calculated as the sum of the grades determined at each visit. Tenderness to palpation was rated on a four-point scale (0 = no pain; 1 = patient stated there is pain; 2 = patient stated there is pain and winces; and 3 = patient stated there is pain and withdraws). The tenderness score was the sum of the number of points obtained during the four visits.

Patients were instructed on the use of pain scales and a functional capacity determination. Patients and physicians used two pain scales. The first was a numerical scale ranging from 0 to 20. On day 1, patients were told to arbitrarily assign 10 to their level of pain; decreases in pain were given numbers below 10 and increasing pain, numbers above 10. The second scale was descriptive, with choices ranging from no pain to severe pain. Mild pain was defined as not too troublesome but needing relief; moderate, very troublesome and needing relief; and severe, extremely troublesome and needing urgent relief. A value from 0 to 3 was assigned to each descriptor. Pa-

tients completed the pain scales daily, and the physicians completed the ratings at each scheduled visit. These values were used to calculate the patient and physician numerical and descriptive pain scores.

The patients also completed a daily functional capacity scale, which ranged from 0 to 3 (0 = usual activities performed without discomfort or difficulty; 1 = usual activities performed with slight discomfort or difficulty; 2 = usual activities performed with great difficulty; and 3 = usual activities could not be performed). The functional capacity score was the total number of points accumulated during the study period.

Patients completed a final assessment of treatment at the end of the 14-day trial or when symptoms resolved and the study medications were no longer required. At the end of the study, each patient rated the overall efficacy of the study medications as excellent to poor, on a scale from 4 to 0. Each patient also graded any remaining limitation of function from none to incapacitating on a scale of 0 to 4, as well as any side effects associated with the drugs.

Statistical Analysis

The Z test for categorical data or Wilcoxon rank sum test for continuous data was used to compare the demographic characteristics of the patients in the two treatment groups at baseline. Between-group outcome measures were compared using the Wilcoxon rank sum test.

RESULTS

The study population comprised 40 patients with acute low back muscle strain associated with muscle spasm. The main

clinical characteristics of the two treatment groups are shown in Table I; the groups were comparable with respect to age, sex, duration of pain before therapy, and proportion of patients with worker's compensation.

When compared with naproxen as monotherapy in the treatment of acute low back strain, the combination of naproxen and cyclobenzaprine resulted in significantly less objective muscle spasm and tenderness ($P<0.05$), as determined by the physician's examination (Table II). Maximum motion of the lumbosacral spine, determined by Schober's test, was significantly greater with combination therapy ($P<0.05$). In addition, with the combined therapy, there were impressive trends toward faster resolution of functional deficits and pain: days to maximum flexion/extension, to resolution of pain, and to sit without pain were all lower after combined therapy, as were the functional capacity scores.

Other measures of functional capacity (including range of motion of the lumbosacral spine) did not differ significantly between the study groups. The total pain scores, as determined by the patients daily and physicians during scheduled visits, were not significantly different.

The overall outcome of treatment in the two groups was similar. The degree of muscle spasm and tenderness was significantly less in patients who received the combination therapy. Although the degree of functional limitation at the conclusion of the study was not statistically different, more patients receiving naproxen alone continued to be symptomatic at the end of the 14-day study period.

The only measure that was more favorable in patients given naproxen alone was side effects (Table III). There were more side effects ($P<0.05$) in the combination group; the most common was

Table I. Clinical characteristics of patients receiving naproxen alone or naproxen plus cyclobenzaprine.

Characteristic	Naproxen	Naproxen plus Cyclobenzaprine
Number of patients	20	20
Age		
Mean	32	37
Range	20-51	26-57
Sex		
Male	13	15
Female	7	5
Duration of pain before treatment (days)		
Mean	2.5	3
Range	1-7	1-10
Number of patients receiving worker's compensation	8	9

drowsiness associated with cyclobenzaprine use.

DISCUSSION AND CONCLUSION

Acute low back pain secondary to muscle strain and associated spasm is a common clinical condition. Muscle strain results from overuse or overstretching of a muscle. An involuntary contraction occurs in the damaged muscle in response to the injury and, in an attempt to limit motion in the damaged area, surrounding undamaged muscles also contract. The inflammatory process is initiated to heal

damaged muscle fibers. As healing progresses, abnormal muscle contraction is diminished and normal motion returns to the damaged area.

There are several treatments to diminish symptoms associated with the healing process. Therapy for muscle strain of the lumbosacral spine includes controlled physical activity, NSAIDs, muscle relaxants, and physical therapy.³ Although muscle relaxants are prescribed frequently, there are relatively few studies² to support their use in patients with muscle strain. Cyclobenzaprine has been reported to be useful in patients with chronic muscle spasm in intractable pain

Table II. Treatment outcome in patients receiving naproxen alone or naproxen plus cyclobenzaprine.

Outcome	Naproxen (n = 20)	Naproxen plus Cyclobenzaprine (n = 20)
Spasm score‡	3	2*
Tenderness score§	3	2.5*
Schober's test		
Maximum score	5	5
Range (cm)	2.0-7.0	4.5-6.0*
Days to maximum anterior flexion/extension	14	7†
Days to resolution of pain		
Patient rating	12.5	8.5†
Physician rating	14	7†
Days to sit without pain	7	5†
Functional capacity	15	9†

* $P < 0.05$.

† $P < 0.10$.

‡Degree of muscle spasm: 0 = none; 1 = mild; 2 = moderate, with loss of reversal of lumbar lordosis; and 3 = severe, with loss of lordosis with abnormal gait

§Degree of tenderness on palpation: 0 = no pain; 1 = patient stated there is pain; 2 = patient stated there is pain and winces; 3 = patient stated there is pain and withdraws.

||Functional capacity: 0 = usual activities performed without discomfort or difficulty, 1 = usual activities performed with slight discomfort or difficulty; 2 = usual activities performed with great difficulty; and 3 = usual activities could not be performed.

Table III. Side effects in patients receiving naproxen alone or naproxen plus cyclobenzaprine.

Side Effect	Naproxen (n = 20)	Naproxen plus Cyclobenzaprine (n = 20)
Drowsiness	0	3
Dyspepsia	1	2
Nervousness	0	2
Abdominal pain	1	0
Constipation	1	0
Headaches	0	1
Dizziness	0	1
Diarrhea	0	1
Dyspepsia and drowsiness	0	1
Dyspepsia and diarrhea	1	0
Dyspepsia and dizziness	0	1
Total	4	12*

* $P < 0.05$ vs naproxen.

syndromes⁶ and in osteoarthritis of the cervical and lumbar spines.⁷ In both studies, patients who took cyclobenzaprine showed statistically significant greater global improvement compared with placebo.

Basmajian⁴ reported the results of a double-blind, 18-center study of 175 patients in which diflunisal versus cyclobenzaprine and the two drugs combined versus placebo were compared. All patients had acute painful spasms of the back of two days' duration or less. Although almost all patients recovered by the tenth day of the study, a statistically significant number of patients had greater clinical improvement with combination therapy. No significant adverse effects attributable to cyclobenzaprine were noted.

The present randomized, open-label study demonstrated a similar beneficial effect of combination therapy compared with NSAID monotherapy. Patients who received the combination therapy had a statistically significantly greater improvement in spasm and tenderness and a greater range of motion during the 14-day study ($P < 0.05$). In addition, there were trends toward more rapid resolution of functional deficits and pain and better functional outcome with combination therapy. Almost twice as many patients remained symptomatic at day 14 in the group receiving naproxen alone.

Side effects were greater with combination therapy. The most common complaint was drowsiness associated with cyclobenzaprine, which was reported by three patients. No side effects, including

drowsiness, were incapacitating, and no patient discontinued the drug because of side effects.

In conclusion, the combination of naproxen and cyclobenzaprine was more effective than naproxen alone in the management of acute muscle spasm associated with acute low back strain. Patients experienced a more rapid decrease

in pain and tenderness as well as greater range of motion with combination therapy.

ACKNOWLEDGMENT

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Expert Opinion

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Aceclofenac in the management of inflammatory pain

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Aceclofenac (Almirall Prodesfarma SA) is an oral NSAID that is effective in the treatment of painful inflammatory diseases and has been used to treat > 75 million patients worldwide. It has proved as effective as diclofenac, naproxen and piroxicam in patients with osteoarthritis, diclofenac, ketorolac, tenoxicam and indomethacin in patients with rheumatoid arthritis and tenoxicam, naproxen and indomethacin in patients with ankylosing spondylitis. It also provides effective analgesia in other indications, such as dental or gynaecological pain, lower back pain and ear, nose and throat indications. Aceclofenac appears to be particularly well-tolerated amongst the NSAIDs, with a lower incidence of gastrointestinal adverse effects. This good tolerability profile results in a reduced withdrawal rate and hence greater compliance with treatment.

Keywords: aceclofenac, arthritis, gastrointestinal, NSAIDs, pain

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1. Overview of the market

Osteoarthritis, rheumatoid arthritis (RA) and ankylosing spondylitis are a group of related, but distinct, disorders of the cartilage of osteoarticular joints.

Osteoarthritis is a degenerative, progressive disorder that predominantly affects the large weight-bearing joints, although other joints can be involved. The clinical characteristics include morning stiffness of short duration, stiffness or 'gelling' on rest, pain on use, joint inflammation and bone deformity. Radiographical changes in the joints may include irregular narrowing of the joint space, subchondral sclerosis and cyst and osteophyte formation. Osteoarthritis is extremely common in the elderly, with an prevalence of 85% in the 75- to 90-year-old population and many patients consider it to be a normal part of the ageing process. Unfortunately, the reduction in mobility caused by osteoarthritis can lead to social isolation, as well as secondary morbidity. In western societies, population changes in age-profile and obesity predict an increasing incidence of osteoarthritis.

RA is less common than osteoarthritis, although no less debilitating. Although RA shares a number of characteristics with osteoarthritis, it is a systemic, rather than a local disease. Swelling and stiffness typically affect the joints of the neck, shoulders, elbows, wrists and especially the proximal joints of the hands. Hips, knees, ankles and toes can also be affected. Unlike osteoarthritis, joints tend to be affected symmetrically and morning stiffness tends to be of longer duration in RA than in osteoarthritis. Systemic symptoms are also common in RA and include fatigue, malaise, subcutaneous nodules (in ~ 20% of patients) and fever.

Ankylosing spondylitis is characterised by inflammation, predominantly of the spine, but in some cases, also of the large peripheral joints. Systemic symptoms can include fever, fatigue and anorexia and in some cases pericarditis and pleuritis may occur.

Taken together, these various forms of rheumatic disorder are responsible for a prodigious burden of morbidity. It is estimated that there are ~ 100 million people suffering from arthritis or other rheumatic disorders across Europe, ~ 14% of the

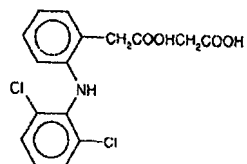


Figure 1. The chemical structure of acetoclofenac.

population [1]. Approximately 50% of these are below the age of retirement, although many retire early due to disability or illness.

Since the introduction of acetylsalicylic acid in the nineteenth century, NSAIDs have become widely used in the treatment of these illnesses for their pain-relieving and anti-inflammatory properties. Given the large and growing numbers of patients affected, NSAID use, both prescription and over-the-counter, is now very common. Although the efficacy of new drugs is well-established, their widespread use has prompted concerns over safety, particularly gastrointestinal (GI), safety and the development and introduction of new NSAIDs has attempted to avoid these problems. The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase, a key enzyme in the inflammation cascade. Cyclooxygenase exists as two isoenzymes:

- COX-1: a constitutive enzyme responsible for the formation of prostacyclin and protective and repair functions in the gastric mucosa.
- COX-2: an inducible enzyme responsible for the generation of inflammatory mediators in response to inflammatory stimuli.

The two isoforms of the enzyme have quite different biological properties and functions. Inhibition of COX-1 is responsible for the potentially serious adverse effects of the NSAIDs.

NSAIDs have varying degrees of specificity for the two isoforms of cyclooxygenase but in recent years there has been a concerted effort to develop COX-2 specific agents in an attempt to avoid the GI tolerability problems that can be manifest during long-term use of NSAIDs.

2. Chemistry

Acetoclofenac is a phenylacetic acid derivative NSAID with a chemical designation of [2-[(2,6-dichlorophenyl)amino]-phenyl]-lactoxyacetic acid]. The chemical structure is shown in Figure 1.

3. Pharmacodynamics

In vitro studies have shown that acetoclofenac inhibits mediators of inflammatory activity, including prostaglandin (PG) E₂, IL-1 β , IL-6 and TNF [2]. Interference with the expression of cell adhesion molecules has also been observed in human neutrophils [3].

Acetoclofenac has also shown stimulatory effects on glycosaminoglycan synthesis in human osteoarthritic cartilage [4] and chondroprotective effects mediated by the suppression of metalloprotease production and proteoglycan release in rabbit articular chondrocytes and human rheumatoid synovial cells [5,6].

Studies using human whole blood assays have shown that acetoclofenac and its metabolite 4'-hydroxyacetoclofenac inhibit COX-2 (IC₅₀ = 0.77 and 36 μ M, respectively) but have relatively little effect on COX-1 (IC₅₀ = > 100 μ M) [7]. These IC₅₀ values represent the concentration required to cause a 50% inhibition of COX; the higher the IC₅₀ value, the less the inhibitory effect of the compound. Diclofenac, another metabolite of acetoclofenac, inhibits both COX-1 and COX-2 (IC₅₀ = 0.6 and 0.04 μ M, respectively). *In vivo* COX-2:COX-1 selectivity has also been demonstrated for acetoclofenac, but not for some other NSAIDs, such as piroxicam, indomethacin, tenoxicam or ketoprofen [8].

In *in vivo* studies in rodents, acetoclofenac alleviated pain and fever and had a lower ulcerogenic potential than naproxen or indomethacin and a similar or lower ulcerogenic potential than diclofenac [9,10].

4. Pharmacokinetics and metabolism

Acetoclofenac is rapidly and completely absorbed following oral administration [2]. Peak plasma concentrations are achieved relatively rapidly (1.25 – 2 h) and the volume of distribution is ~ 25 l. There is no accumulation with regular dosing, with similar maximum plasma concentrations (C_{max}) and time to C_{max} after single and multiple doses. Acetoclofenac is highly bound to plasma proteins (> 99%).

The C_{max}, absorption half-life and volume of distribution of acetoclofenac is not affected by age and therefore dose reductions are generally not necessary in elderly patients [11]. Dose reductions are recommended in patients with hepatic impairment. The presence of food reduces the rate, but not the extent, of absorption of acetoclofenac [12].

Acetoclofenac is metabolised mainly to 4'-hydroxyacetoclofenac, as well as a number of minor metabolites including diclofenac, 5-hydroxyacetoclofenac, 5-hydroxydiclofenac and 4'-hydroxydiclofenac [13]. The main route of elimination is via the urine (70 – 80%), mainly as the glucuronides of acetoclofenac and its metabolites. The elimination half-life is ~ 4 h.

No important drug interactions have been identified with acetoclofenac; those that have been observed are similar to those seen with other NSAIDs. These include interactions with anticoagulants, cyclosporin, diuretics, quinolone antibiotics, lithium, digoxin and methotrexate.

5. Clinical efficacy

5.1 Osteoarthritis

Osteoarthritis is a progressive degenerative condition characterised by joint pain, tenderness, inflammation and restriction

Table 1. Double-blind, controlled studies assessing the efficacy of aceclofenac in patients with osteoarthritis.

N; type of osteoarthritis	Treatment	Duration	Rating instruments	Results	Ref.
397; knee	AC 100 mg b.i.d. DI 50 mg t.i.d.	12 weeks	Investigator assessment of joint pain at rest Joint tenderness, joint effusion, erythema, pain on movement Stiffness, night pain, pain intensity at rest, weight-bearing pain by patient	Similar significant improvement in both groups in investigators' assessments. Patients' assessments: pain relief significantly better with AC	[17]
59; knee and hip	AC 100 mg b.i.d. DI 50 mg t.i.d.	28 days	Pain VAS (Huskisson's)	Similar significant improvement in pain severity in both groups	[18]
335; knee	AC 100 mg b.i.d. DI 50 mg t.i.d.	6 months	LOSI Knee function (extension and flexion)	Similar significant improvements in LOSI and pain in both groups	[19]
240; knee	AC 100 mg b.i.d. PI 20 mg/day	2 months	LOSI Knee function (subjective score) Knee function (goniometer) Pain VAS	Similar significant improvements in both groups on the LOSI and pain	[20]
205; knee	AC 100 mg b.i.d. PI 20 mg/day	3 months	Pain VAS SIG Functional capacity (flexion or extension of knee)	Similar significant improvements in pain, severity and knee extension and flexion in both groups	[21]
374; knee	AC 100 mg b.i.d. NA 500 mg b.i.d.	12 weeks	Investigator assessment of pain Knee flexion (goniometer) Patient assessment of pain intensity, nocturnal pain, pain at rest	Similar significant improvements in pain, joint swelling, joint stiffness and knee function in both groups	[22]

AC: Aceclofenac; DI: Diclofenac; LOSI: Lequesne Osteoarthritis Severity Index; N: Number of patients; NA: Naproxen; PI: Piroxicam; SIG: Severity index of gonarthritis; VAS: Visual analogue scale.

in movement. It occurs most commonly in the elderly and the condition is almost universal in those > 80 years of age [14,15]. Amongst Europeans > 65 years of age, it is estimated that at least 50% have radiological signs and 12.5% have a clinical diagnosis of osteoarthritis [16].

Aceclofenac has been proved to be at least as effective as other NSAIDs, including diclofenac, piroxicam and naproxen, in reducing the pain and severity of symptoms and improving functional capacity in patients with osteoarthritis (Table 1) [17-22].

Two large double-blind studies have compared aceclofenac with diclofenac, both of which were carried out in patients with osteoarthritis of the knee. In the first study (n = 397), there was a significant (p = 0.0001) improvement in pain intensity from baseline in both groups after 12 weeks, as assessed by the investigator on a five-point pain score scale, with 75 and 70% in the aceclofenac and the diclofenac group, respectively, showing improvement [17]. The other investigator assessments, including joint tenderness, swelling, pain on movement, functional capacity and overall assessment, also revealed a similar significant improvement with both treatments. However, there was a trend towards greater improvement in complete knee movement and reduced pain on movement with aceclofenac and patients with initial flexion deformity experienced a significantly greater improvement in knee flexion with aceclofenac than with diclofenac. The patients' subjective assessment of pain relief also revealed

a significant advantage for aceclofenac, with 71% of patients reporting an improvement in pain intensity compared with 59% in the diclofenac group (p = 0.005) [18]. In the second study (n = 335), both treatments resulted in a similar significant improvement in the Lequesne Osteoarthritis Severity Index (LOSI) and pain evaluated on a Visual Analogue Scale (VAS) after 15 days versus baseline (p < 0.001) [19,18]. From 100% baseline values, the OSI was reduced at the end of the study to 55 and 57% with aceclofenac and diclofenac, respectively, and the pain VAS score to 54% in both groups. Significant improvements were also observed in knee function and knee flexion; these effects were maintained over the 6-month study.

Aceclofenac has also been compared with piroxicam in two large double-blind studies in patients with osteoarthritis of the knee. In a 2-month study, similar significant improvements versus baseline in pain intensity and functional capacity of the knee, as assessed by the OSI, were seen with aceclofenac and piroxicam in 240 patients (p < 0.001) [20]. This was supported by significant improvement in the patients' assessment of pain intensity using a VAS (p < 0.001) and the investigators' assessments of knee function, extension and flexion (p < 0.01). However, the improvement in knee flexion was more rapid with aceclofenac than with piroxicam, with significant effects occurring after 2 weeks of aceclofenac treatment, but only after 1 month of piroxicam treatment. Similar results were reported in the other study (n = 205), with significant

Acetclofenac

Table 2. Double-blind, controlled studies assessing the efficacy of acetclofenac in patients with rheumatoid arthritis.

N	Treatment	Duration	Rating instrument	Results	Ref.
169	AC 100 mg b.i.d. KE 50 mg t.i.d.	3 months	Pain VAS RI Grip strength Subjective assessment of morning pain Duration of morning stiffness Functional capacity according to Steinbrokers criteria	Similar significant improvements in RI, pain, grip strength, morning stiffness and pain, pain on movement, nocturnal pain and functional capacity	[24]
55	AC 100 mg b.i.d. KE 50 mg t.i.d.	6 months	RI Spontaneous morning pain, pain on movement, nocturnal pain (unspecified) Duration of morning stiffness Handgrip strength Functional capacity (unspecified)	AC faster acting than KE, AC more effective than KE in improving pain at rest, pain on movement and RI	[25]
343	AC 100 mg b.i.d. DI 50 mg t.i.d.	6 months	Pain VAS RI Duration of morning stiffness Grip strength	Similar significant improvements in pain, RI, handgrip and morning stiffness	[26]
219	AC 100 mg b.i.d. IN 50 mg b.i.d.	12 weeks	Number of painful and swollen joints Duration of morning stiffness Grip strength ARA functional class Investigator and patient global assessment	Similar significant improvements in the number of painful and swollen joints, grip strength, duration of morning stiffness, pain intensity and functional class in both groups	[22]
237	AC 100 mg b.i.d. TX 20 mg/day	3 months	RI Grip strength Number of patients with morning stiffness Pain VAS	Similar significant improvements in RI, grip strength, morning stiffness and pain intensity in both groups	[28]

AC: Acetclofenac; ARA: American Rheumatism Association; DI: Diclofenac; IN: Indomethacin; KE: Ketoprofen; LOSI: Lequense Osteoarthritis Severity Index, N: Number of patients; RI: Ritchie index; SIG: Severity index of gonarthritis; TX: Tenoxicam; VAS: Visual analogue scale.

improvements in pain (VAS), severity index for gonarthritis and knee flexion and extension in both groups ($p < 0.01$) [21].

Finally, acetclofenac proved as effective as naproxen in 374 patients, again with osteoarthritis of the knee [22]. Both treatments resulted in significant improvements in pain at rest, pain on movement and pain from pressure on the joint ($p < 0.05$), with an improvement in overall pain being reported in 76 – 86% of patients. This was accompanied by a reduction in joint swelling and stiffness and an improvement in knee function. Functional capacity was improved in 81 and 84% of acetclofenac- and naproxen-treated patients, respectively. An overall improvement of the condition was seen as early as week 2 in 56% of patients treated with acetclofenac and 48% treated with naproxen. At the end of the study, the investigators reported an overall improvement in 73 and 69% of patients in the acetclofenac and the naproxen group, respectively.

5.2 Rheumatoid arthritis

RA is a chronic condition characterised by inflammation of the peripheral joints of the feet, hands, wrists, ankles and elbows. It affects ~ 1% of the population in Europe, is two to three times more common in women than in men and tends to first manifest itself at ~ 30 years of age [23].

Double-blind studies have confirmed that the efficacy of acetclofenac in patients with RA is at least comparable to that

of ketoprofen, indomethacin, diclofenac and tenoxicam (Table 2) [24-28].

A relatively small, double-blind study indicated that acetclofenac was more effective and faster acting than ketoprofen in patients with RA [24,25]. However, a subsequent larger study failed to prove any clear superiority of acetclofenac over ketoprofen, although the improvement was again more rapid, with a significant reduction in the Ritchie Index (RI) (evaluation of joint tenderness) occurring after 15 days ($p < 0.001$) with acetclofenac, but not until 1 month with ketoprofen ($p < 0.05$) [19,25]. All other parameters, including pain (VAS), grip strength, morning stiffness and pain, pain on movement, nocturnal pain and functional capacity, were improved similarly with both treatments. A total of 4 patients in the acetclofenac group and 11 in the ketoprofen group, withdrew from the study prematurely due to inefficacy. Similar differences in favour of acetclofenac compared with other NSAIDs have been reported in terms of withdrawal due to adverse events and hence overall acceptability (see Section 6) [19,29].

A double-blind study in 343 patients showed that acetclofenac and diclofenac were equally effective in improving pain (VAS), morning stiffness, RI and handgrip [26]. The overall assessment of efficacy by the patient and investigator at the end of the study was good to very good in 70 and 76% of cases, treated with acetclofenac and 66 and 70% of cases

Table 3. Double-blind, controlled studies assessing the efficacy of aceclofenac in patients with rheumatoid arthritis.

N	Treatment	Duration (months)	Rating instruments	Results	Ref.
273	AC 100 mg b.i.d. TX 20 mg/day	3	Duration of morning stiffness Pain VAS Objective mobility assessment indices	Similar significant improvements in morning stiffness, pain, modified Schöber's test, C7-iliac crest distance, lateral flexion of the spine, thoracic expansion and occiput-wall distance	[30]
126	AC 100 mg b.i.d. NA 500 mg b.i.d.	3	Pain VAS Pain on movement Pain at rest Chest expansion Hand-to-floor distance Schöber's test Capacity to perform normal daily activities	Similar significant improvement in spontaneous pain, pain on movement and at rest, chest expansion, hand-to-floor distance, Schöber's test and normal daily activities	[31,32]
310	AC 100 mg b.i.d. IN 25 mg b.i.d. and 50 mg/day	3	Pain VAS Morning stiffness Modified Schöber's test C7-iliac crest line measurement Patient global assessment	Similar significant improvements in pain, morning stiffness, modified Schöber's test, C7-iliac crest distance and lateral spine flexion	[32]

AC: Aceclofenac; IN: Indomethacin; N: Number of patients; NA: Naproxen; TX: Tenoxicam; VAS: Visual analogue scale.

treated with diclofenac, respectively. Similarly, in a comparison with indomethacin in 219 patients, the improvements in the number of painful and swollen joints, grip strength, duration of morning stiffness, pain intensity and American Rheumatism Association (ARA) functional class were comparable with both treatments [22,27].

5.3 Ankylosing spondylitis

Ankylosing spondylitis is characterised by inflammation of the spine and large peripheral joints. Patients suffer from cyclical back pain and morning stiffness, as well as systemic symptoms such as fever, fatigue, weight loss and anaemia. The prevalence in Europe is estimated to be 0.2 – 1%, and the condition is more common in men than in women and amongst those with a family history of the disorder.

Aceclofenac has been proved to be as effective as naproxen, tenoxicam and indomethacin in double-blind studies carried out in patients with ankylosing spondylitis (Table 3) [30-32].

When compared with tenoxicam in a 3-month, double-blind study in 273 patients, aceclofenac was as effective in improving morning stiffness, pain (VAS), the modified Schöber's test, the C7-iliac crest distance, lateral flexion of the spine, thoracic expansion and the occiput-wall distance [30]. Aceclofenac tended to be superior, with regard to occiput-wall distance, whilst there was a trend in favour of tenoxicam in lateral spinal flexion and thoracic expansion. Both drugs were rated as 'good' at the end of the study, with morning stiffness improving by 68 and 65% in the aceclofenac and tenoxicam groups, respectively, and the pain VAS score improving by 45% in both groups. There were no significant differences between the groups regarding the need for additional paracetamol.

In another 3-month, double-blind study that enrolled 126 patients, aceclofenac and naproxen both resulted in

similar improvements in spontaneous pain (VAS), pain on movement, pain at rest, chest expansion, hand-to-floor distance and the Schöber's test [31]. Most patients in both groups also improved their capacity to perform normal daily activities, with no significant differences between the two treatments. At the end of the study, the overall efficacy assessment by the physician and the patients was similar for the two groups.

Aceclofenac was also compared with indomethacin in a 3-month study that enrolled 310 patients [32]. Pain (VAS), morning stiffness, modified Schöber's test, C7-iliac crest distance and lateral spine flexion all improved significantly with both drugs, with no significant differences between the groups. The pain VAS score and morning stiffness improved by 37 and 51%, with aceclofenac and 41 and 46%, with indomethacin, respectively. Other variables including chest expansion, occiput-wall distance, Likert pain score, use of paracetamol rescue and the patient and physician global assessment also showed similar significant improvements from baseline.

5.4 Analgesic effects

A small, double-blind study (n = 12) compared the effects of aceclofenac and diclofenac on PGE₂ levels in the synovial fluid of patients suffering from acute knee pain with synovial effusion [33]. Both aceclofenac 75 mg t.i.d. and diclofenac 50 mg t.i.d. resulted in a progressive marked reduction in joint pain and an improvement in joint function during the 6-day study, although the effect was somewhat more rapid with aceclofenac. Only aceclofenac resulted in a significant reduction in synovial fluid levels of PGE₂ from baseline (113.0 – 66.8 pg/ml).

It is estimated that ~ 80% of the European population will experience back pain lasting for at least 1 day at some time during their lives [34]. In many of these, the problem with recur

Acetoclofenac

and will be associated with considerable morbidity. Acetoclofenac (150 mg b.i.d. i.m. for 2 days + 100 mg b.i.d. p.o. for 5 days) was also more effective than diclofenac (75 mg b.i.d. i.m. for days + 50 mg t.i.d. p.o. for 5 days) in 100 patients with acute lumbago, as assessed by the physicians' overall assessment of efficacy, alleviation of functional impairment and pain (VAS) [35]. The physician's assessment of efficacy was at least good in 85% of acetoclofenac-treated patients, compared with 76% of those given diclofenac ($p < 0.05$). In a larger, double-blind study, in 227 patients with acute lower back pain, acetoclofenac 100 mg b.i.d. and diclofenac 75 mg b.i.d. resulted in a similar significant improvement in pain at rest (VAS), with a trend towards a greater improvement with acetoclofenac [36]. After 8–10 days, the mean change in pain score at rest compared with baseline was 61.6 mm with acetoclofenac and 57.3 mm with diclofenac. The change in the mean pain score on movement versus baseline was also greater with acetoclofenac (61.4 mm) than with diclofenac (56.7 mm). Improvements in functional impairment and ability to perform routine daily activities were also greater in the acetoclofenac group. A total of six patients in the acetoclofenac group, but only one in the diclofenac group, withdrew prematurely due to early cure.

In two comparative studies, involving a total of 99 patients, acetoclofenac 100 mg was shown to be more effective than paracetamol 650 mg in the relief of postepisiotomy pain [37,38]. Single doses of acetoclofenac 100 or 150 mg have been shown to provide effective analgesia in patients with moderate-to-severe dental pain and those undergoing third molar extraction [39–41]. Other indications in which acetoclofenac has proved effective include dysmenorrhoea and musculoskeletal trauma such as contusions and sprains [42–44].

6. Safety and tolerability

6.1 General safety

Apart from those associated with the GI system, the most common adverse events seen with acetoclofenac are dizziness, vertigo, pruritus, rash and dermatitis. However, these events occur in only a small proportion of patients and the overall tolerability profile of acetoclofenac has been shown to be similar to that of placebo in patients with rheumatic disorders [45]. Elevated liver enzymes occur in ~2.5% of patients, which is a similar incidence to that observed with other NSAIDs, such as diclofenac, indomethacin, naproxen, piroxicam and tenoxicam. Other non-GI adverse effects are very rare, typically occurring with frequencies of <1%.

A large, 12-month, prospective, community-based study complying with the Safety Assessment of Marketed Medicines (SAMM) guidelines has been carried out in patients with osteoarthritis, RA or ankylosing spondylitis [29]. A total of 10,142 patients were enrolled, 7890 of whom were treated with acetoclofenac 100 mg b.i.d., and 2252 with diclofenac 75 mg b.i.d. The overall incidence of adverse events was significantly lower with acetoclofenac than with diclofenac ($p < 0.001$), as was the percentage of patients discontinuing the study due to

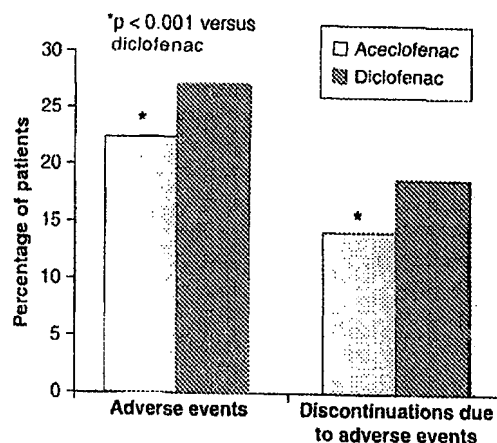


Figure 2. Individual incidence of overall adverse events and discontinuations due to adverse events with acetoclofenac and diclofenac in patients enrolled in the SAMM study [29]. SAMM: Safety Assessment of Marketed Medicines

adverse events ($p < 0.001$) (Figure 2). There were no reports of any serious hepatic adverse events in either group.

In double-blind, controlled studies, the overall incidence of adverse events was significantly lower with acetoclofenac than with naproxen (45 versus 55 events; $p = 0.025$) in 374 patients with osteoarthritis [22], and than with indomethacin (42 versus 75 events; $p = 0.006$) in 219 patients with RA [27]. In another comparison with naproxen, the overall tolerability of acetoclofenac was rated as significantly better by physicians and patients ($p < 0.05$) [32]. In another comparison with indomethacin, there was no difference in the overall incidence of adverse events, although CNS symptoms (mainly headache and dizziness) were significantly less common with acetoclofenac (2.6 versus 13.7%; $p < 0.001$) [32]. The percentage of patients discontinuing treatment due to adverse events was also significantly lower with acetoclofenac than with ketoprofen (2.3 versus 13.4%; $p < 0.01$) in 169 patients with RA [24] and than with diclofenac (8.2 versus 16.4%; $p < 0.05$) in 335 patients with osteoarthritis [19].

In a meta-analysis of 13 double-blind, randomised studies involving 3574 patients with osteoarthritis, RA or ankylosing spondylitis, those receiving acetoclofenac were 1.38 times (95% CI = 1.19–1.60; $p < 0.001$) more likely to be free of adverse events than those taking other NSAIDs (diclofenac, indomethacin, naproxen, piroxicam, tenoxicam or ketoprofen) [46]. In addition, the number of withdrawals due to adverse events was also significantly lower with acetoclofenac than with the comparator NSAIDs (odds ratio 0.67; 95% CI = 0.52–0.86; $p = 0.002$).

In terms of hepatic safety, acetoclofenac may elevate circulating levels of hepatic enzymes; the incidence of such elevations is similar to that seen with diclofenac, indomethacin, naproxen, piroxicam and tenoxicam [2].

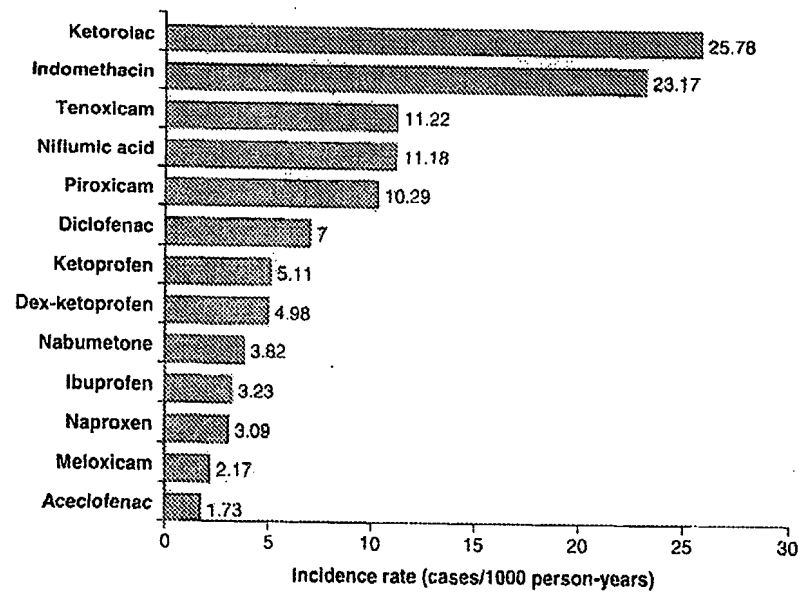


Figure 3. Incidence rate (cases per 1000 person-years) of upper gastrointestinal bleeding with NSAIDs [48].

7. Gastrointestinal safety and tolerability

GI adverse events, such as nausea, diarrhoea, flatulence, constipation, vomiting, bleeding and ulcers, are the most common tolerability problems with all NSAIDs. However, evidence indicates that aceclofenac has a particularly good GI tolerability profile.

In the previously discussed SAMM study [29], the most common adverse events in both groups were GI-associated. However, the overall incidence of GI adverse events was significantly lower with aceclofenac than with diclofenac (10.6 versus 15.2%; $p < 0.001$), as was the incidence of the four most common adverse events: dyspepsia (5.4 versus 6.7%; $p = 0.017$), abdominal pain (2.5 versus 4.4%; $p < 0.001$), diarrhoea (1.5 versus 3.6%; $p < 0.001$) and nausea (1.6 versus 2.4%; $p = 0.01$). In addition, the incidence of nausea, abdominal pain and diarrhoea leading to discontinuation was, respectively, 46, 65 and 41 lower with aceclofenac than with diclofenac ($p < 0.001$).

The effect of aceclofenac and diclofenac on the gastroduodenal mucosa has been specifically studied endoscopically in a double-blind, placebo-controlled study in 30 healthy volunteers [47]. Endoscopic findings were graded according to the modified Lanza score. Following administration of placebo, aceclofenac 150 mg/day or sodium diclofenac 75 mg/day for 2 weeks, there was significantly more gastropathy in the diclofenac group than in the aceclofenac and placebo groups ($p < 0.05$). No significant differences were observed between the aceclofenac and placebo groups. Gastric mucosal content of hexosamine, a factor that is known to have a protective effect on cells and gastroduodenal blood flow were also significantly reduced by diclofenac. It has been suggested that

impairment of mucosal microcirculation might play an important role in NSAID gastropathy. In contrast, aceclofenac significantly increased hexosamine content and had no effect on blood flow. Similarly, in a 10-day double-blind study in 12 healthy volunteers, diclofenac 50 mg t.i.d. resulted in a significant increase in GI blood loss (0.59 ml) whilst the increase with aceclofenac (0.29 ml) was not significant [48].

Superior GI tolerability of aceclofenac compared with diclofenac has also been reported in double-blind, controlled trials in patients with rheumatic disorders [17,19,26-36]. Similar advantages for aceclofenac in terms of GI adverse events are seen in double-blind studies with other NSAIDs. For example, in a comparison of aceclofenac and piroxicam in 205 patients with osteoarthritis, GI intolerance was reported by twice as many piroxicam-treated as aceclofenac-treated patients (14 versus 7) [21,22]. In another comparison with piroxicam ($n = 240$), there were twice as many reports of faecal blood loss in the piroxicam group than in the aceclofenac group [20]. A significantly higher incidence of withdrawals due to GI adverse events was reported with ketoprofen than with aceclofenac (9 versus 1; $p < 0.01$) in 169 patients with RA [24]. In the meta-analysis of 13 studies discussed in the previous section [46,48], patients taking aceclofenac were 1.52 times more likely to be free of GI adverse effects than those receiving comparator NSAIDs (95% CI = 1.29 - 1.80; $p < 0.001$) and the incidence of withdrawals due to GI effects was 52.5% lower (95% CI = 0.34 - 0.65; $p < 0.001$).

A specific, population-based analysis has recently been carried out to compare the incidence of upper GI bleeding between 13 various NSAIDs [49]. Data were collected over a 4-year period from 180,995 patients in a Spanish health

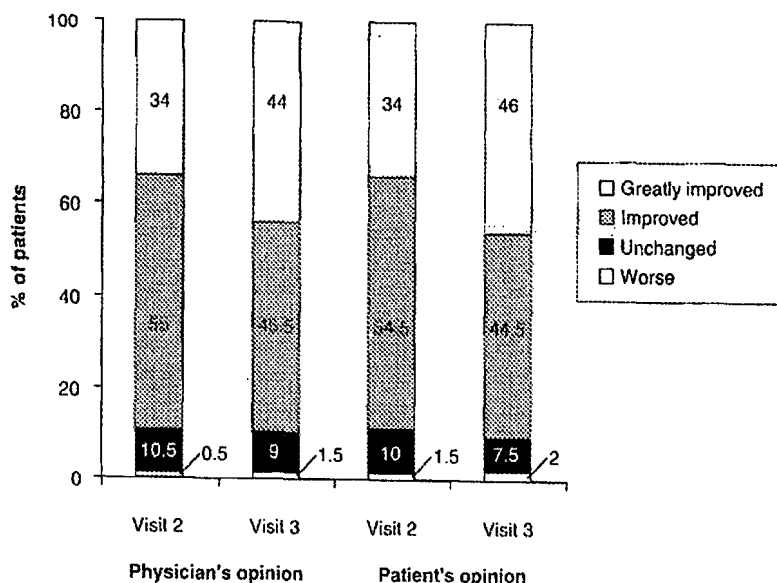


Figure 4. Evaluation of status by the physician and the patient amongst patients suffering from acute post-traumatic pain [50].

authority area. The incidence of upper GI bleeding varied markedly, ranging from 1.7 for acetoclofenac to 25.8/1000 person-years for ketorolac (Figure 3). Taking acetoclofenac as the reference to assess the relative risk for each NSAID, those with a relative risk of ≥ 4 (i.e., diclofenac, piroxicam, niflumic, tenoxicam, indomethacin and ketorolac) were considered to be statistically worse than acetoclofenac. Thus, acetoclofenac had the lowest risk of upper GI tract bleeding.

8. Compliance

As many patients with rheumatic disorders will require long-term therapy, it is essential that medications are well-tolerated, as well as effective, in order to ensure good compliance. Therefore, a pan-European observational cohort study has recently been conducted in order to determine whether the good tolerability profile of acetoclofenac is associated with good patient acceptability [50]. A total of 23,407 patients who were treated with acetoclofenac for pain, due to various inflammatory or degenerative rheumatic diseases, were asked to evaluate their treatment in terms of pain evolution, patient overall status and overall satisfaction with treatment. Physician evaluations were also performed for patient overall status and compliance. The patients considered acetoclofenac to be a highly effective treatment, with fast and prolonged analgesic effects. The patient overall status was considered improved or much improved in 84% of cases, > 94% of patients were compliant with treatment and 93.5% expressed overall satisfaction at the final visit (visit 3). These findings were similar irrespective of whether the pain was acute, semichronic or chronic.

However, the greatest treatment difference was seen amongst patients suffering from acute disease, such as post-traumatic pain (Figure 4).

These findings support those from the meta-analysis of 13 double-blind, randomised studies involving > 3500 patients with osteoarthritis, RA or ankylosing spondylitis [46]. Patients treated with acetoclofenac were significantly more likely to complete the treatment than those treated with diclofenac, indomethacin, naproxen, piroxicam, tenoxicam or ketoprofen (odds ratio 1.37; 95% CI = 1.17 – 1.60; $p < 0.001$). When the data were analysed according to disease, this significant difference remained for osteoarthritis and RA, although not for ankylosing spondylitis. As discussed previously, the number of withdrawals due to adverse events and GI adverse events was significantly lower with acetoclofenac than with the comparator NSAIDs.

9. Cost-effectiveness

Although acetoclofenac is similar in terms of efficacy to other NSAIDs, its superior tolerability and compliance indicate that there may be economic consequences. A decision analytical model was therefore constructed using data from 12 double-blind randomised trials conducted in patients with osteoarthritis, RA or ankylosing spondylitis [51]. Despite substantial differences in drug acquisition costs (US\$0.18 – 0.73/day), there were no significant differences between acetoclofenac and the comparator NSAIDs (diclofenac, indomethacin, ketoprofen, naproxen and tenoxicam) in terms of total costs, although piroxicam was significantly less expensive overall and

iatrogenic costs were lower for aceclofenac than for comparators. This was attributable to the considerably lower iatrogenic costs associated with aceclofenac (i.e., costs related to treatment of adverse events and substitution treatment after NSAID discontinuation), even though the cost of acquisition was higher for aceclofenac than for the other NSAIDs. Although there are criticisms of this type of study [52] and some of the results appear anomalous, the study does suggest that the higher cost of aceclofenac is more than compensated for by its reduced iatrogenic effects.

10. Expert opinion

The NSAID market is undoubtedly crowded and competitive, with new compounds being introduced frequently and older drugs being almost as frequently withdrawn or relabelled. In order to prosper, medications in this area in particular need to offer specific and tangible benefits. Diclofenac is the gold-standard medication for inflammatory arthritic conditions, being both effective and inexpensive, although its tolerability lags behind the best of the newer drugs. Although a new drug in some markets, aceclofenac has been used in clinical practice for > 10 years. It is registered in > 60 countries worldwide and around 75 million patients have been treated, and in excess of 1 billion defined daily doses administered. Depending on the country, aceclofenac may be available as tablets, sachets, a cream and an injection.

It is within this context that the place of aceclofenac in therapy needs to be considered, not only in terms of its absolute efficacy, safety, tolerability and compliance, but also when measured against the therapeutic alternatives, particularly diclofenac.

The objective of drug treatment in osteoarthritis, RA and ankylosing spondylitis is to reduce inflammation, ameliorate pain and improve joint function and mobility. On this basis, it is clear from the foregoing analysis that the overall efficacy of aceclofenac is equivalent to that of diclofenac in osteoarthritis and RA, to naproxen in osteoarthritis and ankylosing spondylitis, to indomethacin in RA and ankylosing spondylitis and to piroxicam in osteoarthritis, to ketoprofen and tenoxicam in RA, and tenoxicam in ankylosing spondylitis. This is not unexpected as all of the NSAIDs are potent inhibitors of cyclooxygenase. Although there is a general lack of differential efficacy between all of the NSAIDs, this does not mean

that they are all equivalent to each other in terms of efficacy; variations in individual patient responses to NSAIDs require a degree of adaptation of therapy to find the best solution for each patient [53,54]. The differing efficacy and adverse effect profile of the various NSAIDs allow therapy to be better tailored to the individual needs of the patient.

Given their broadly equivalent efficacy, the key issues for NSAIDs are safety and tolerability, particularly their propensity to cause upper GI bleeding. In this respect, aceclofenac appears to have an advantage over the majority of other NSAIDs. A meta-analysis of 13 double-blind, randomised, controlled studies indicated that aceclofenac had the lowest incidence of upper GI bleeding of any of the agents included in the analysis [46]. In comparative studies, even where the rate of GI symptoms was equivalent, there were generally fewer withdrawals due to side effects with aceclofenac than with comparator agents. Endoscopic studies, although their applicability to the clinical situation has been questioned, confirm that aceclofenac causes less gastromucosal damage than diclofenac [47]. The large, community-based study SAMMs showed a statistically significant advantage for aceclofenac compared with a sustained release preparation of diclofenac [29]. A further postmarketing study comprising of > 180,000 patients also showed that aceclofenac had the lowest incidence of upper GI effects of any of the 13 NSAID medications included [49].

Upper GI bleeding, pain and discomfort are the predominant adverse effects of all NSAIDs and, as well as being potentially life-threatening, can frequently lead to interruption or cessation of treatment. The improved safety profile of aceclofenac in this respect contributes not only to better patient acceptability, but better compliance as well. Thus, when compared with other NSAIDs, patients treated with aceclofenac can expect not only fewer GI adverse effects, but to be able to tolerate their medication better and consequently benefit from better control of their symptoms.

Overall, short- and medium-term studies show that aceclofenac is as effective as other NSAIDs and in particular is comparable in this respect with the gold-standard diclofenac. In contrast, the GI tolerability of aceclofenac appears to be not only as good as the best of the alternative NSAIDs but also significantly better than the majority. This has been shown to result in better patient acceptability and hence better compliance [50].

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Estudo multicêntrico do uso de aceclofenaco no tratamento de traumas músculo-esqueléticos

Multicenter, open study of the use of aceclofenac 100 mg, twice a day, in the treatment of muscular-skeletal traumas

RESUMO

Em 12 centros nacionais foram tratados 120 pacientes portadores de entorses ou distensões com aceclofenaco por via oral, 100 mg, duas vezes ao dia. Após sete dias de tratamento 74,60% dos pacientes com entorse e 80,70% com contusão estavam assintomáticos e receberam alta. Em apenas dois pacientes o tratamento foi ineficaz e em 10% dos casos houve aparecimento de eventos adversos.

INTRODUÇÃO

O aceclofenaco, sintetizado há dez anos (Sainsz Olalla, 1988), é um analgésico antiinflamatório não-esteróidal (AINEs), que tem demonstrado boa tolerância, tendo sido testado em casos de artrite reumatóide, artrose e outros processos dolorosos (Sainz Olalla, 1988; Movília, 1989; Peris e cols, 1996; Lederman, 1997 e Marques Neto, 1997).

O presente estudo é o primeiro a ser feito em casos de traumas músculo-esqueléticos no país e no exterior em nível de fase IV, o qual tem a finalidade de confirmar o valor terapêutico, encontrar eventos adversos, padrões de utilização da droga e descobrir novas indicações, adotando os princípios de GCP (Good Clinical Practice), na qual as pesquisas clínicas são desenhadas, implantadas e relatadas, envolvendo os eventos adversos, consentimento informado, o manuseio dos produtos investigacionais e dos documentos do estudo.

CASUÍSTICA

Foram avaliados 121 pacientes com traumas músculo-esqueléticos medica-

dos com aceclofenaco. Os pacientes foram divididos em dois grupos: grupo E = pacientes com entorse e grupo C = pacientes com contusão.

No grupo E (entorse) foram incluídos 63 pacientes sendo, 21 (33,3%) do sexo feminino e 42 (66,6%) do sexo masculino e no grupo C (contusão) 58 pacientes, sendo 9 (15,5%) do sexo feminino e 49 (84,5%) do sexo masculino.

A idade em ambos os grupos variou de 14 a 73 anos (média de 32,7), sendo a etnia branca predominante em 56 (88,9%) dos pacientes no grupo E e 46 (79,3%) no grupo C.

Na avaliação inicial dos pacientes a frequência cardíaca, pressão arterial, altura e peso estavam dentro dos padrões considerados normais. Doze pacientes (10%) estavam em tratamento de outras patologias, portanto, faziam uso de outros medicamentos que foram mantidos até o final da avaliação.

No grupo E o predomínio da localização do trauma foi o tornozelo em 29 casos (46%) e o joelho foi o segundo local mais frequente em 14 casos (22,2%). No grupo C o joelho e a mão foram comprometidos em nove casos (15,5%) cada um (Tabela 1).

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TABELA 1
Localização

	Entorse N (%)	Contusão N(%)
Ombro	1 (1,59%)	4 (6,90%)
Quadril	1 (1,59%)	1 (1,72%)
Cervical	2 (3,17%)	1 (1,72%)
Coxa	1 (1,59%)	1 (1,72%)
Cotovelo	2 (3,17%)	5 (8,62%)
Joelho	14 (22,22%)	9 (15,52%)
Lombar	1 (1,59%)	1 (1,72%)
Antebraço	1 (1,59%)	3 (5,17%)
Tornozelo	29 (46,03%)	3 (5,17%)
Gradeado costal	0 (0,00%)	3 (5,17%)
Punho	1 (1,59%)	5 (8,62%)
Perna	0 (0,00%)	3 (5,17%)
Mão	0 (0,00%)	9 (15,52%)
Pé	7 (11,11%)	5 (8,62%)
Dedo da mão	3 (4,76%)	5 (8,62%)
Outros	0 (0,00%)	3 (5,17%)
Total	63 (100,00%)	58 (100,00%)

A causa da lesão no grupo E foi queda accidental em 24 casos (38,1%) e decorrente de prática esportiva em 23 casos (36,5%), sendo que no grupo C a queda accidental foi relatada em 25 casos (43%) e prática esportiva em 13 casos (22,4%).

Dentre as práticas esportivas, o futebol foi responsável por 21 casos (80,77%) no grupo E e em nove (75%) no grupo C.

Todos os pacientes foram avaliados em no máximo 72 horas da ocorrência do trauma, sendo que a média foi de 20 horas.

Quando indicado os pacientes realizavam fisioterapia ou imobilização do local lesado, sendo que a imobilização foi utilizada em 39 casos (61,9%) no grupo E e 30 (51,7%) no grupo C.

MÉTODOS

Foram avaliados 121 pacientes divididos em 12 centros nacionais ligados ao ensino e à pesquisa. Destes, apenas um paciente não preencheu os seguintes critérios de inclusão:

- a) Idade entre 18 e 80 anos;
- b) Portador de lesão tipo entorse ou con-

tusão tendo sido a menos de 72 horas e que não tenham sido submetidos a nenhuma cirurgia; e

- c) Mulheres quando em idade fértil deveriam apresentar exame de gravidez (sanguíneo ou urina) negativo.

Dentre os pacientes selecionados foram excluídos os que apresentassem os seguintes critérios:

- a) Patologias cardíacas, hepáticas, renais, neurológicas, hematológicas e/ou respiratórias;
- b) História prévia de broncoespasmo ou opressão precordial provocada por AINEs;
- c) Hipersensibilidade prévia a outros AINEs;
- d) Diagnóstico de úlcera gástrica no decorrer do último ano e/ou episódios anteriores de perfuração gástrica ou duodenal e/ou gastrectomia ou outra cirurgia;
- e) Fratura ou instabilidade articular decorrente do traumatismo no segmento em estudo;
- f) Mulheres grávidas ou lactantes;
- g) Participação em outros estudos clínicos nos últimos três meses.

O aceclofenaco foi utilizado, por via oral, sendo um comprimido de 100 mg, duas vezes ao dia, durante 14 dias, e foram realizadas duas avaliações nos dias 7 e 14, podendo ter sido considerado curado na primeira avaliação (sétimo dia). Quando necessário, a área lesada poderia ser imobilizada e/ou o paciente poderia ser submetido à fisioterapia.

O paciente poderia suspender a medicação, em qualquer fase do tratamento.

Durante as duas visitas os pacientes foram avaliados quanto à eficácia e tolerabilidade ao aceclofenaco, assim como, exame físico geral e específico. A eficácia do aceclofenaco foi avaliada através dos seguintes critérios:

- 1) Evolução dos níveis de dor pela escala visual analógica de dor;
- 2) Evolução dos níveis de dor pela escala de dor semiquantitativa em quatro graus (sem dor, dor leve, moderada ou intensa);
- 3) Evolução da inflamação da área afetada pela avaliação de edema, hematoma e necrose, podendo ser classificado em ausente e presente (obrigatoriamente retirava-se a imobilização para avaliação);
- 4) Evolução da incapacidade funcional através da escala semiquantitativa em quatro graus (normal, impotência funcional leve, moderada e total);
- 5) Avaliação geral do tratamento pelo pesquisador e pelo paciente;
- 6) A tolerabilidade foi avaliada pelo aparecimento espontâneo de sintomas no paciente e pela observação do pesquisador.

Concomitante à avaliação da eficácia e da tolerabilidade foram relatados os eventos adversos quanto a sua origem e à relação com a droga em estudo.

RESULTADOS

Foram avaliados os resultados do tratamento, a tolerância ao medicamento e os efeitos adversos.

Em relação à eficácia do medicamento foram avaliadas a dor, a impotência funcional e a presença de edema e hematoma. As Tabelas 2,3,4 e 5 e o Gráfico 1 mostram a evolução desses itens entre o atendimento inicial (visita 1) e o retorno após uma semana (visita 2),

como ainda após duas semanas (visita 3) nos casos que tiveram que ser medicados por mais tempo. A avaliação da tolerância pelo médico e pelo paciente ao medicamento nos retornos (visitas 2 e 3) está demonstrada nas Tabelas 6 e 7.

Eventos adversos ocorreram em dez casos (Tabela 8), sendo graves em apenas dois, um paciente apresentou gastrite por quatro dias e a droga foi suspensa. O outro teve queimação estomacal e a dose foi reduzida. Em nenhum dos casos o evento foi considerado grave. Um terceiro paciente teve diarreia por três dias, o evento foi considerado de intensidade moderada, mas a droga foi suspensa. Um outro paciente teve coriza por oito dias, que foi de intensidade leve, não foi atribuída à droga, mas a dosagem foi reduzida.

No grupo "entorse" 47 pacientes (74,60%) e no grupo "contusão" 46 (80,70%) receberam alta após a primeira semana, mesmo persistindo alguma dor leve.

Finalmente, o médico e o paciente avaliaram subjetivamente o resultado do tratamento. Observa-se nas Tabelas 9 e 10, que apenas dois pacientes, tanto na opinião do médico como na do pacien-

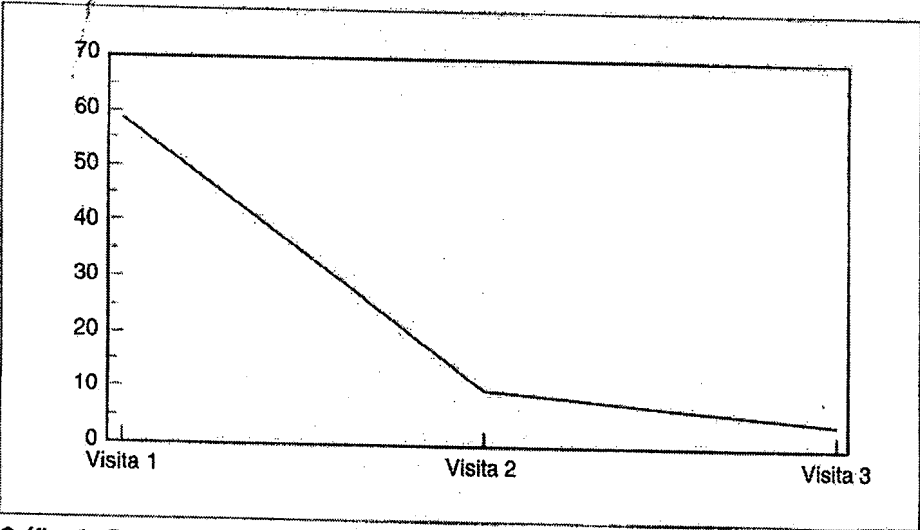


Gráfico 1 - Escala visual analógica da dor.

TABELA 2
Escala de edema semiquantitativa de três graus

	ENTORSE			CONTUSÃO		
	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)
Ausente	7 (11,11)	44 (69,84)	13 (82,86)	11 (18,97)	48 (84,21)	8 (88,89)
Moderado	38 (60,32)	17 (26,98)	1 (7,14)	39 (67,24)	9 (15,79)	1 (11,11)
Grande	18 (28,57)	2 (3,17)		8 (13,79)		
Total	63	63	14	58	57	9
	X² = 47,66		P < 0,0001*	X² = 49,94		P < 0,0001*

TABELA 3
Escala de dor semiquantitativa de quatro graus

	Entorse			Contusão		
	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)
Ausente		39 (61,90)	13 (92,86)		37 (64,91)	7 (77,78)
Leve	3 (4,76)	19 (30,16)	1 (7,14)	11 (18,97)	17 (29,82)	2 (22,22)
Moderada	35 (55,56)	4 (6,35)		25 (44,83)	2 (3,51)	
Intensa	25 (39,68)	1 (1,59)		21 (36,20)	1 (1,75)	
Total	63	63	14	58	57	9
	X² = 97,43		P < 0,0001*	X² = 76,06		P < 0,0001*

TABELA 4
Escala de Impotência funcional semiquantitativa de quatro graus

	ENTORSE			CONTUSÃO		
	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)
Capacidade normal	0 (0,00)	41 (65,08)	13 (92,86)	2 (3,45)	42 (73,68)	9 (100,00)
Impotência leve	12 (19,05)	17 (26,93)	1 (7,14)	17 (29,31)	13 (22,81)	0 (0,00)
Impotência moderada	42 (66,67)	4 (6,35)	—	28 (48,28)	2 (3,51)	—
Impotência total	9 (14,29)	1 (1,59)	—	11 (18,97)	—	—
Total	63	63	63	58	57	9
	$\chi^2 = 79,65$	$P < 0,0001^*$		$\chi^2 = 70,43$	$P < 0,0001^*$	

TABELA 5
Hematoma

	ENTORSE			CONTUSÃO		
	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)	Visita 1 N (%)	Visita 2 N (%)	Visita 3 N (%)
Ausente	41 (65,08)	54 (85,71)	13 (92,86)	41 (71,93)	54 (94,74)	9 (100,00)
Presente	22 (34,92)	9 (14,29)	1 (7,14)	16 (34,92)	3 (5,26)	0 (0,00)
Total	63	63	14	57	57	9
	$\chi^2 = 6,16$	$P = 0,0131^*$		$\chi^2 = 9,09$	$P = 0,0025^*$	

TABELA 6
Avaliação da tolerância pelo médico

	ENTORSE		CONTUSÃO	
	Visita 2 N (%)	Visita 3 N (%)	Visita 2 N (%)	Visita 3 N (%)
Boa	49 (77,78)	1 (7,14)	44 (78,57)	3 (33,33)
Excelente	11 (17,46)	13 (92,96)	11 (19,64)	6 (66,67)
Regular	2 (3,17)	—	1 (1,79)	—
Má	1 (1,59)	—	—	—
Total	63	14	56	9
	$\chi^2 = 30,35$	$P < 0,0001^*$	$\chi^2 = 8,91$	$P = 0,0116^*$

TABELA 7
Avaliação da tolerância pelo paciente

	ENTORSE		CONTUSÃO	
	Visita 2 N (%)	Visita 3 N (%)	Visita 2 N (%)	Visita 3 N (%)
Excelente	55 (87,30)	13 (92,86)	45 (81,82)	6 (66,67)
Boa	5 (7,94)	0 (0,00)	9 (16,36)	3 (33,33)
Regular	1 (1,59)	1 (7,14)	1 (1,82)	0 (0,00)
Má	2 (3,17)	—	—	—
Total	63	14	55	9

te, não melhoraram e um paciente piorou no grupo E, não prosseguindo o tratamento. Dos 23 pacientes que necessitaram de uma segunda semana de tratamento (terceira visita), apenas um não apresentou melhora significativa.

DISCUSSÃO

Aceclofenaco é um antiinflamatório não-hormonal (AINH) relacionado ao diclofenaco e foi submetido a 56 investigações clínicas, sendo 24 estudos duplo-cegos em casos de artrose, artrite reumatóide e espondilite anquilosante e 14 destes eram estudos de fase III, incluindo mais de 3800 pacientes. A droga foi comparada com diclofenaco, naproxeno, piroxicam, cetoprofeno, tenoxicam e indometacina, mostrando ser pelo menos tão eficaz quanto os outros AINHs, causando menos reações adversas (Peris e cols., 1996). Tratando-se de afecções crônicas e de tratamentos relativamente prolongados de pelo menos um mês,

TABELA 8
Eventos adversos

	ENTORSE		CONTUSÃO	
	Visita 2 N (%)	Visita 3 N (%)	Visita 2 N (%)	Visita 3 N (%)
Não presente	55 (87,30)	12 (85,71)	53 (92,98)	9 (100,00)
Presente	8 (12,70)	2 (14,27)	4 (7,02)	—
Total	63	14	57	9

TABELA 9
Pacientes em relação ao início do estudo (segundo o médico)

	ENTORSE		CONTUSÃO	
	Visita 2 N (%)	Visita 3 N (%)	Visita 2 N (%)	Visita 3 N (%)
Muito melhor	57 (90,48)	14 (100,00)	53 (96,36)	9 (100,00)
Um pouco melhor	4 (6,35)	—	1 (1,82)	—
Nenhuma mudança	1 (1,59)	—	1 (1,82)	—
Um pouco pior	1 (1,59)	—	—	—
Total	63	14	55	9

TABELA 10
Paciente em relação ao início do estudo (segundo o paciente)

	ENTORSE		CONTUSÃO	
	Visita 2 N (%)	Visita 3 N (%)	Visita 2 N (%)	Visita 3 N (%)
Muito melhor	50 (79,37)	14 (100,00)	47 (85,45)	8 (88,89)
Um pouco melhor	11 (17,46)	—	7 (12,73)	1 (11,11)
Nenhuma mudança	1 (1,59)	—	1 (1,82)	—
Um pouco pior	1 (1,59)	—	—	—
Total	63	14	55	9

considerou-se interessante avaliar a eficácia em um estudo controlado (fase IV e GCP) para uma afecção aguda, tal como um traumatismo músculo-esquelético (contusão e entorse) durante um período curto, de uma a duas semanas. Os 121 pacientes pertenciam a dois grupos: entorse e contusão, no entanto, em relação aos objetivos do estudo, ou seja, avaliar a eficácia, tolerabilidade e incidência e gravidade dos eventos adversos, os dois grupos foram unidos. Predominou o sexo masculino em ambos os gru-

pos, fato esperado em tratando-se de traumatismo músculo-esquelético. É interessante notar que 46% dos entorses eram do tornozelo e 22% do joelho, enquanto as contusões atingiam predominantemente o joelho (15,5%) e a mão (15,5%). Em ambos os grupos a causa principal foi queda acidental, seguida do esporte, predominando aqui o futebol. O protocolo do estudo previa a suspensão do medicamento antes do sétimo dia, caso os sintomas desaparecessem. Apesar de serem controlados os

comprimidos e contados em cada retorno, não foi possível conseguir que todos os pacientes devolvessem os comprimidos restantes, caso tivessem suspendido o tratamento antes de completar sete dias. A contagem dos comprimidos no retorno daria uma maior confiabilidade à avaliação da adesão ao tratamento. Quanto à eficácia, observou-se que após sete dias 92,06% do grupo entorse e 94,73% do grupo contusão se apresentaram sem dor ou com dor leve; dos pacientes que necessitaram uma semana adicional 1 de 14 no grupo entorse e 2 de 7 no grupo contusão (respectivamente, 7,14% e 22,22%) tinham apenas dor leve, o restante não sentindo dor na avaliação final. A impotência funcional e o edema regrediram em porcentagens muito semelhantes. Não foi possível avaliar em quanto tempo a medicação surtia efeito, mas observou-se que 74,6% dos pacientes com entorse e 80,7% com contusão tiveram alta após sete dias. A falta de eficácia no tratamento foi observada em apenas dois casos, sendo que um deles, não tendo melhorado na primeira semana não prosseguiu com o medicamento. Esses índices de eficácia estão muito acima dos relatados pelos autores no tratamento de condições crônicas (Lederman, 1997; Ximenes, 1997; Marques Neto, 1997). Observou-se uma incidência de 10% de efeitos adversos, sendo a metade relacionada com o trato digestivo. Este valor corresponde a uma incidência 50% menor do que nos casos crônicos (Ximenes, 1997). Mesmo assim, apenas dois pacientes interromperam a medicação, comparando favoravelmente com os casos crônicos com 7,69% (Ximenes, 1997).

CONCLUSÃO

O estudo demonstrou que em lesões traumáticas agudas o aceclofenaco age rapidamente, tem uma eficácia muito grande e é bem tolerado. No curto espaço de tempo que este tratamento foi

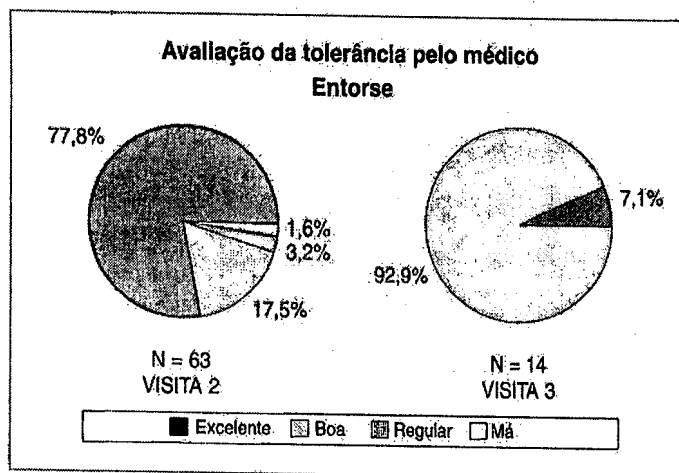


Gráfico 2

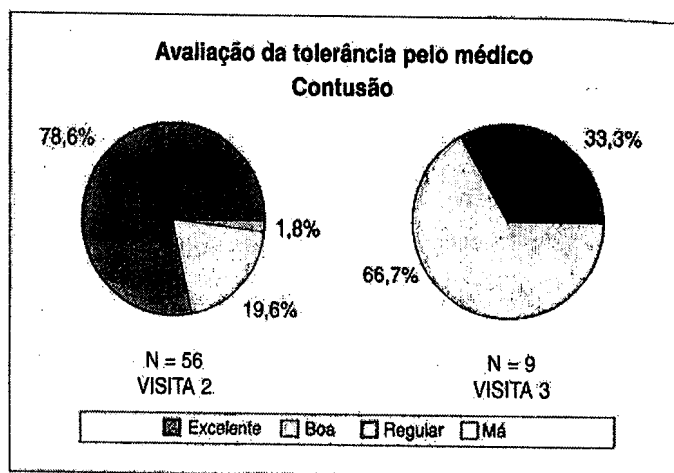


Gráfico 3

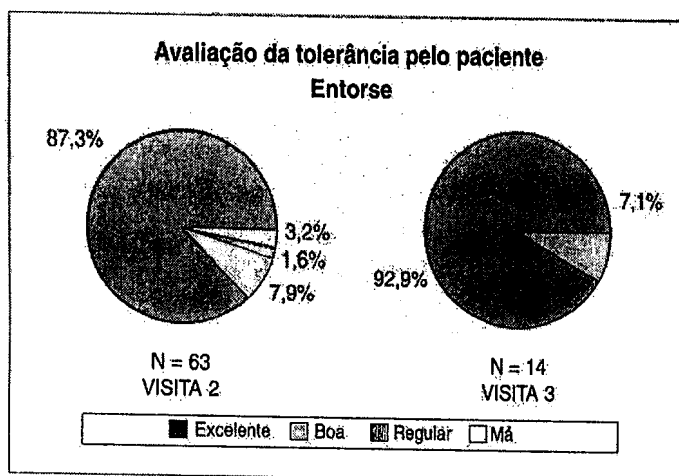


Gráfico 4

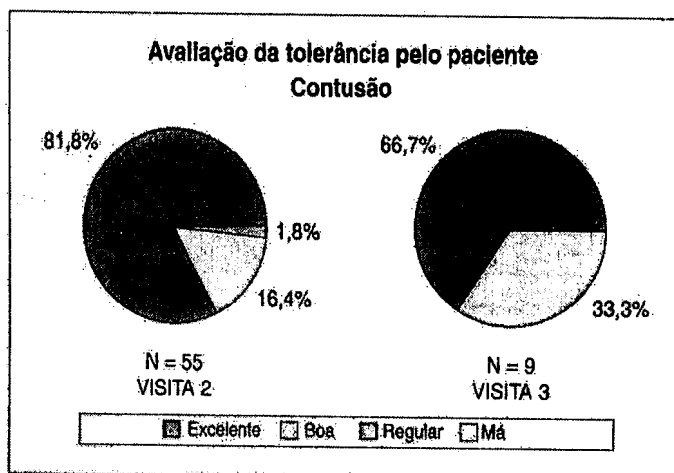


Gráfico 5

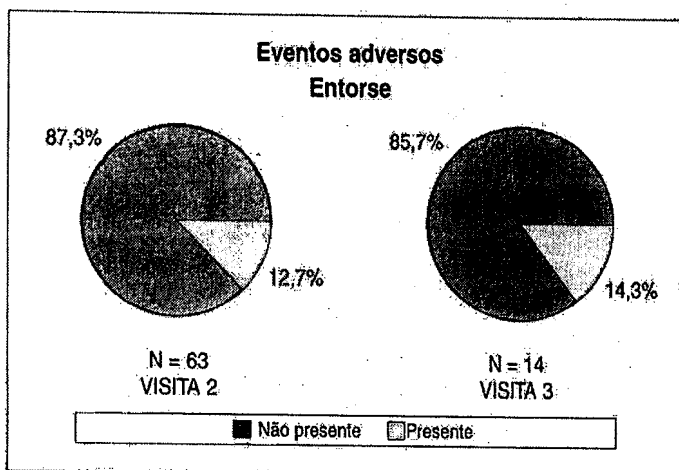


Gráfico 6

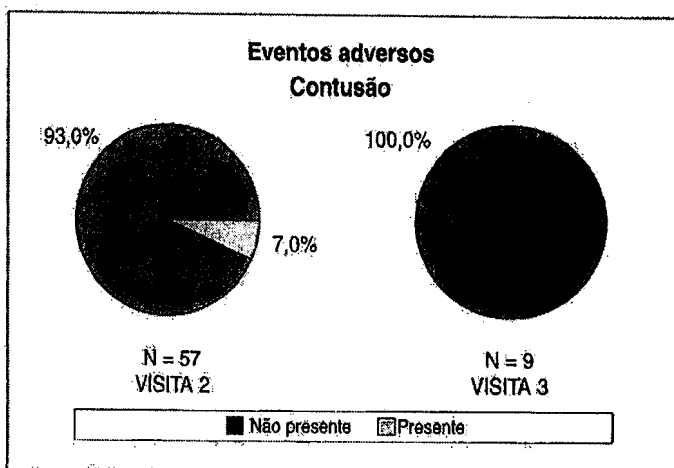


Gráfico 7

prescrito, o abandono causado por efeitos adversos especialmente com referência ao sistema digestivo, foi mínimo, sendo ao redor de 2%.

SUMMARY

In 12 centres 120 patients with articular sprain or contusion were treated

with aceclofenac, 100 mg b.i.d., orally. After 7 days of treatment 74,60% of the patients with sprains and 80,70% with contusions were asymptomatic and

were discharged. Only 2 patients had no benefit from the treatment and in 10% of the cases adverse effects appeared.

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AN - EMB-1998130679

TI - Multicenter, open study of the use of aceclofenac 100 mg, twice a day, in the treatment of muscular-skeletal traumas

AB - In 12 centres 120 patients with articular sprain or contusion were treated with aceclofenac, 100 mg b.i.d., orally. After 7 days of treatment 74,60% of the patients with sprains and 80,70% with contusions were asymptomatic and were discharged. Only 2 patients had no benefit from the treatment and in 10% of the cases adverse effects appeared.

KW - adolescent; adult; aged; article; clinical trial; common cold: side effect; contusion: drug therapy; diarrhea: side effect; drug efficacy; drug tolerability; female; gastritis: side effect; good clinical practice; human; human tissue; major clinical study; male; multicenter study; musculoskeletal injury(#): diagnosis, drug therapy, epidemiology; oral drug administration; sprain: drug therapy

- aceclofenac(#): adverse drug reaction, clinical trial, drug therapy, pharmacology; nonsteroid antiinflammatory agent(#): adverse drug reaction, clinical trial, drug therapy, pharmacology

PUB - Revista Brasileira de Medicina

- 1998

- br

AU - Koberle G; Magalhaes A A C; Pocco C A J; Caetano E B; Dos Reis F B; Filho G R M; Musafir M E; Falavinha R S; Canto R S D T; Goncalves R K; Drumond S N; Targa W H D C

ADAF - Hospital das Clinicas, Unicamp, Sao Paulo

IPN - ISSN 0034-7264 (print)

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PG - 63 - 69

DT - Journal, Article

TFT - Drug Literature Index; Adverse Reactions Titles; Internal Medicine

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AN - EMB-2000231751

TI - Study of the efficacy and tolerability of BRISTAFLAM(R) (aceclofenac) in the treatment of inflammatory and/or painful processes of musculoskeletal and joint diseases

AB - Objective: To assess the efficacy, tolerability and safety of BRISTAFLAM(R) in the treatment of inflammatory and/or painful musculoskeletal and joint diseases. Design: An open study of oral 100 mg twice daily BRISTAFLAM(R) in 963 patients for 30 days. Setting: 175 investigators dealing with musculoskeletal and joint diseases in six university medical centers in Egypt participated in the study. Subjects: Nine hundred and sixty three patients of whom 43% were males, ages ranged between 18-80 years with acute painful inflammatory or increase in intensity of chronic musculoskeletal or joint diseases were allocated to the study. Results: There were significant improvements in muscular and joint pain, in stiffness and in daily activity. Adverse events reported were mainly due to gastrointestinal affection, occurred in 9.79% and were a cause of withdrawal from the study in 1.5% of patients. Conclusion: In a short-term treatment for one month, BRISTAFLAM(R) was effective in painful joint and musculoskeletal diseases with wide margin of safety.

IN - adult; aged; arthritis(#): drug therapy; arthropathy(#): drug therapy; article; clinical trial; daily life activity; drug efficacy; drug safety; drug tolerability; dyspnea: side effect; edema: side effect; Egypt; epigastric pain: side effect; female; gastritis: side effect; hot flush: side effect; human; joint stiffness; major clinical study; male; multicenter study; muscle fatigue: side effect; nausea: side effect; rash: side effect; treatment outcome; vomiting: side effect

- aceclofenac(#): adverse drug reaction, clinical trial, drug therapy, oral drug administration; bristaflam; nonsteroid antiinflammatory agent: adverse drug reaction, clinical trial, drug therapy, oral drug administration

AW - bristaflam

PUB - Journal of Clinical Research

- 1999

- gb

AU - El-Ghobarey A F; El-Badawy S; Khaled A R

AUAF - 18 Elserganey Street, AbdouPasha, Abbasia, Cairo

IRN - ISSN 1369-5207 (print)

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DT - Journal, Article

TFT - Arthritis and Rheumatism; Drug Literature Index; Adverse Reactions Titles