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ORIGINAL ARTICLE

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The efficacy and tolerability of aceclofenac compared to indomethacin in patients with rheumatoid arthritis

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Abstract The efficacy and tolerability of aceclofenac (100 mg bid; $n = 109$), a new non-steroidal anti-inflammatory agent, was compared to that of indomethacin (50 mg bid; $n = 110$) in a multi-centre, 12-week, randomized, double-blind clinical trial in patients with rheumatoid arthritis. The efficacy of aceclofenac, on the basis of several clinical features characteristic for rheumatoid arthritis, was comparable to that of indomethacin. Patients in both treatment groups showed a notable and significant improvement during the study. Under aceclofenac treatment, the number of painful and swollen joints decreased by a median of six and nine, respectively, morning stiffness was shortened by 1 h, and the grip strength of both hands increased by a median of 8 mmHg. Pain at rest was relieved in 65.3% of aceclofenac-treated patients and in 67.1% of those treated with indomethacin (n.s.). With regard to safety, aceclofenac tended to be better tolerated than indomethacin. Among the 109 aceclofenac-treated patients, 26 incidents of adverse effects due to the drug were noted in 20 patients (18.4%). Sixty-four incidents of adverse events were documented in 32 (29.1%) of the 110 patients treated with indomethacin. The most common adverse events reported during treatment with aceclofenac were heartburn (four patients) and vertigo (three patients).

Key words Aceclofenac · Indomethacin · Rheumatoid arthritis · Pain · Morning stiffness

Introduction

Rheumatoid arthritis is the most common rheumatic disease and the most prevalent disorder of the joints and connective tissue seen in daily clinical practice [1]. The main objective of therapy is to halt or reduce joint inflammation in order to maintain the patient's mobility. The classic therapeutic approach consists of physical therapy, the administration of non-steroidal anti-inflammatory drugs (NSAIDS) and the initiation of basic treatment with the long-term goal of halting the progression of the disease.

Aceclofenac, 2-[(2,6-dichlorophenyl)amino] phenyl acetoxy-acetate, is a new member of the phenylacetic acid class of NSAIDs [2], which includes diclofenac. The results of clinical trials conducted to date confirm that aceclofenac is effective in the treatment of acute pain resulting from tooth extraction and episiotomy as well as in the long-term treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and scapulo-humeral periarthritis [3–10]. In two trials in which the safety of aceclofenac was compared to that of diclofenac, it was found that the gastric tolerance of aceclofenac tended to be greater [4, 11]. In two comparative studies in rheumatoid arthritis, aceclofenac was found to be as effective and at least as well tolerated as ketoprofen [10, 12].

The following is a report on the results of a trial comparing aceclofenac with indomethacin in patients with rheumatoid arthritis.

Patients and methods

Patients

This study was a 12-week, multi-centre (30 centres in Germany), randomized, double-blind clinical trial comparing two parallel groups and was conducted in accordance with the Guidelines for Good Clinical Practice (GCP) and with the Declaration of Helsinki. Included in the study were male and female outpatients aged 18–75 years with rheumatoid arthritis. The inclusion criteria for each patient were rheumatoid arthritis with a minimum of four of the diagnostic criteria of the American Rheumatism Association (ARA) [13] and a doc-

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umented medical history of a therapeutic response to NSAIDs (including aspirin) during the previous year. The patients had to be in an active stage of the disease and exhibit a minimum of three of the following symptoms: six or more joints painful or sensitive during movement; three or more swollen joints; morning stiffness lasting an hour or longer; C-reactive protein levels equal to or greater than 0.7 mg/dl. In addition, the patients had to be in Steinbrocker progression stages I, II or III [13] functional class I, II or III of the ARA. Exclusion criteria included rheumatic disease other than rheumatoid arthritis, gastrointestinal disease, active gastrointestinal ulcers, gastrointestinal bleeding, serious hepatic disorders or kidney dysfunction, blood disorders, asthma and alcohol or drug abuse. Not included in the clinical trial were patients who were receiving anticoagulants, barbiturates, sulfonylureas, diuretics or ACE inhibitors. Also excluded from participation were pregnant women and females of child-bearing age not using adequate contraception, as well as patients with a known sensitivity or allergy to other NSAIDs or other analgesic drugs.

Treatment

Patients who met all of the initial inclusion criteria during the 14-day examination period preceding the start of the study, were randomized to receive tablets of either 100 mg aceclofenac or 50 mg indomethacin. They were instructed to take two tablets daily – one with a liquid or food upon rising and the other approximately 12 h later – for a period of 12 weeks. During the wash-out phase and the first 2 weeks of treatment only, patients were permitted to take one or two paracetamol tablets (500 mg) up to a maximum of four times daily as needed. Patients who were receiving therapy with gold salts, D-penicillamine, anti-malarial drugs, corticosteroids or sulphasalazine were allowed to continue taking these drugs provided that they had started taking them at least 24 months prior to the start of the trial and that they continued taking them for the duration of the study. Patients who had started physical therapy before entering the study were permitted to continue with it. Any changes in physical therapy routine during the study were to be noted.

Study procedure

The following clinical assessments were made at the end of weeks 2, 4, 8 and 12 to evaluate the study treatment: the number of painful and swollen joints, the duration of morning stiffness, grip strength, ARA functional class and the investigator's and the patient's global evaluation of the disease (on a scale of 1 to 5, with 1 being very good). Both the physician and the patient assessed pain intensity. The physician rated rest pain as 1 (none), 2 (mild), 3 (moderate), 4 (severe) or 5 (very severe), whereas the patient gave his or her assessment on a 10-cm visual analogue scale (VAS). During the last visit, a full physical examination was completed and documented, C-reactive protein levels were tested and the patient was assigned to a Steinbrocker progression stage. To evaluate tolerability, the patients were asked direct questions. Their responses and their voluntary and spontaneous comments as to the number, the degree and the duration of adverse effects were documented and tabulated. Laboratory tests, including blood chemistry and urine analysis, were completed, and vital signs, such as blood pressure and pulse, were checked and documented at the end of the 2nd week and at the conclusion of the trial after 12 weeks. Any changes in other medication and any other illness were documented, and a compliance check on the remaining tablets was also made during these assessment visits.

Statistical analysis

The non-parametric patient data were analysed statistically using Fisher's exact test or the chi-squared test, the Wilcoxon test and the Mantel-Haenszel test. Student's *t*-test was applied to parametric data. The efficacy data from all patients who received trial medication were analyzed on an intention-to-treat basis. Patients who failed to complete the trial and protocol violators were excluded from the per protocol analysis. In addition, an end-point analysis was performed on data from all patients at their final visit, regardless of whether they had completed the 12 weeks of treatment.

Results

Of the 223 patients enrolled in the study, 219 were randomly assigned to one of the two study groups. One hundred and nine patients received aceclofenac and 110 patients received indomethacin as the study medication (Table 1). There was no significant difference between the two groups with regard to medical history or clinical parameters examined before the start of the study. Approximately 90% of the patients had been suffering from rheumatoid arthritis for more than 1 year (Table 2). Recent past medication – in most cases diclofenac – was documented for 83 patients (76.2%) of the aceclofenac group and 86 patients (78.2%) of the indomethacin group. Fourteen patients (11.6%) of the aceclofenac group and 13 patients (11.6%) of the indomethacin group continued to receive their gold salt medication for the duration of the study. Twenty-one patients (19.4%) of the aceclofenac group and 22 patients (20.2%) of the indomethacin group continued to receive physical therapy.

Two hundred and nineteen patients were included in the intention-to-treat analysis. There were 39 protocol violators who were not included in the per protocol analysis. Significantly more patients ($P<0.05$) in the aceclofenac group (97 patients, 89%) than in the indomethacin group (83 patients, 75.5%) completed the study. Deteriorating condition was the main reason for drop-out, accounting for 13 patients (12%) of the indomethacin group and 6 patients (5.5%) of the aceclofenac group.

With the noted exceptions, the following data are based on the intention-to-treat analysis. No significant difference was found between the groups for this or any of the following per protocol and end-point analyses. The statistical evaluation indicated that there was no significant difference in the compared efficacy of the two drugs.

Table 1 Gender and age of patients (intention-to-treat analysis)

	Aceclofenac	Indomethacin
Number of subjects	109	110
Males	31 (28.4%)	33 (30.0%)
Females	78 (71.6%)	77 (70.0%)
Median age (years)	56	56
Interquartile range	49–63	49–61

Table 2 History of rheumatoid arthritis (intention-to-treat analysis)

Time since onset (years)	Aceclofenac		Indomethacin	
	n	%	*n*	%
<1	9	8.26	14	12.73
1–5	30	27.52	37	33.64
6–10	28	25.69	18	16.36
11–15	16	14.68	15	13.64
≥15	26	23.85	26	23.64

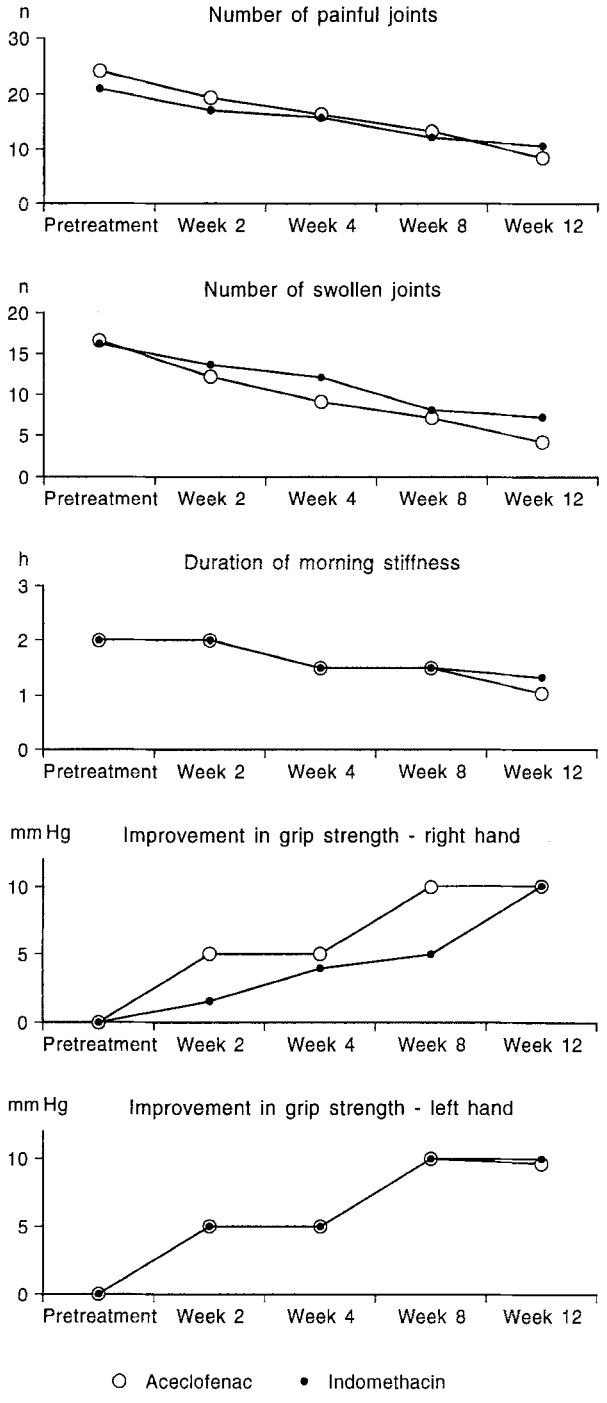

Fig. 1 Clinical assessments over time (median values; intention-to-treat analysis)

Total number of painful and swollen joints

As can be seen in Fig. 1 and Table 3, there was clear and significant ($P<0.05$) improvement in both medication groups over the course of the treatment. While a median 24 joints were painful and 16.5 were swollen at the start of the treatment in the aceclofenac group, only 8 and 4 joints (median value), respectively, were affected at the end of the treatment. The number of affected joints in the indomethacin group decreased from 21 to 10 painful joints and from 16 to 7 swollen joints.

Table 3 Clinical parameters: change in values from pretreatment to end point

Change	Aceclofenac	Indomethacin
Median number of painful joints	–9*	–6*
Interquartile range	(–20)–(–2)	(–16)–(–1)
Median number of swollen joints	–6*	–6*
Interquartile range	(–16)–(–2)	(–11)–(–1)
Grip strength (mmHg)		
Right hand median	8*	10*
Interquartile range	(–1.5)–(20)	(–5)–(20)
Left hand median	8*	10*
Interquartile range	(–0.5)–(20)	(0)–(20)
Duration of morning stiffness (h)	–1.0*	–0.7*
Interquartile range	(–1.5)–(0.3)	(1.5)–(0)
Pain intensity (mm VAS)	–22.6±27.6	–18.9±26.7

* $P<0.05$ (end-point analysis)

Grip strength

Grip strength in both hands was significantly ($P<0.05$) and comparably improved in both the aceclofenac and the indomethacin groups, by 8 and 10 mmHg, respectively (Table 3, Fig. 1).

Duration of morning stiffness

Significant improvements over the initial or pretreatment values were observed in both treatment groups (Fig. 1). The median duration of morning stiffness was reduced by 1 h in the aceclofenac group and by 0.7 h in the indomethacin group from the initial or pretreatment value of 2 h (Table 3).

Pain intensity at rest (patient's assessment)

The patients rated their pain at rest using a 10-cm VAS: 0 mm = no pain to 100 mm = excruciating pain. The VAS reduction in pain at rest tended to be greater in the aceclofenac group than in the indomethacin group (Table 3).

Pain intensity at rest (physician's assessment)

As can be seen in Fig. 2, before the study approximately half of the patients in each group complained of moderate pain, while over a quarter complained of severe or very severe pain. These proportions were significantly reduced ($P<0.01$) during the course of treatment. A reduction in pain intensity or an improvement was documented in 65.3% of the aceclofenac cases and 67.1% of the indomethacin cases. The proportion of patients who experienced a worsening of pain at rest was less than 10% in each group.

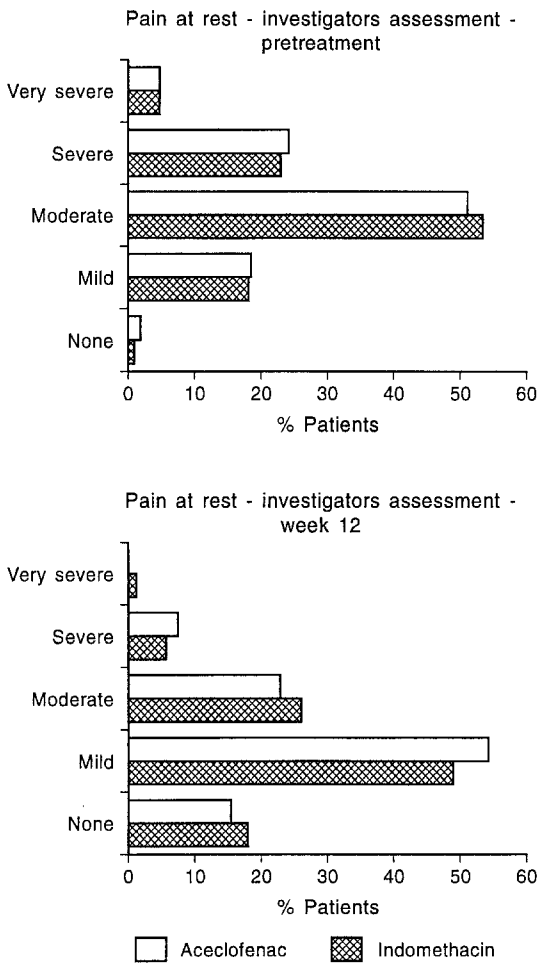

Fig. 2 Pain at rest, investigator's assessment (intention-to-treat analysis; *n* pretreatment/week 12: aceclofenac 108/96, indomethacin 109/88)

ARA functional classes

Intention-to-treat analysis showed an improvement in the Steinbrocker or ARA class from pretreatment to week 12 in 27% of the patients in each group. The condition or classification of 71% of the patients in each group remained unchanged. A deterioration was noted in only two patients in each group.

Global evaluation

As shown in Fig. 3, the investigators noted similar results for both medication groups. An overall improvement from the time of admission until the final visit assessment was reported in two-thirds of the patients treated. The patients' own assessment was consistent with this finding. Compliance (% dose taken) was excellent, with 99% of the patients in each group taking the medication dispensed to them.

Drug safety

The drug sagety evaluation was based on the documented adverse events and their analysis as well as on the results

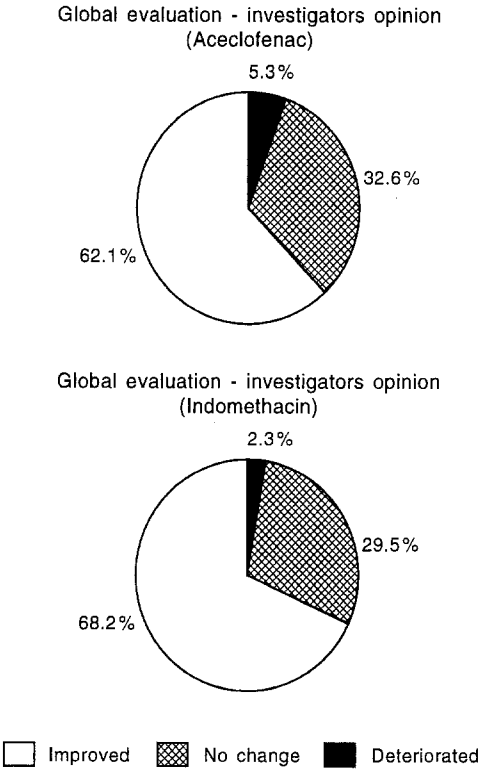

Fig. 3 Global evaluation, change from pretreatment (intention-to-treat analysis; aceclofenac $n=95$, indomethacin $n=88$)

of the laboratory tests and the recorded values for vital signs. No clinically relevant changes in the vital signs (pulse and blood pressure) were found in either of the two treatment groups. During the treatment period 30 patients in the aceclofenac group reported 42 adverse events, while 42 patients in the indomethacin group reported 75 adverse events. Patients in the aceclofenac group reported a higher incidence of heartburn ($n=6$), whereas patients in the indomethacin group more often reported vertigo ($n=13$) and nausea ($n=9$). Patients in the indomethacin group reported a greater number of adverse events affecting a greater number of patients ($P=0.0063$). Twenty-six of the 42 adverse events reported by the aceclofenac group and 64 of 75 of the adverse events in the indomethacin group were at least possibly related to the medication (Table 4). As summarized in Table 4, heartburn (3.7%) and vertigo (2.8%) were the most common adverse drug reactions in the aceclofenac group. The most common adverse drug reactions in the indomethacin group were vertigo (11.8%) and nausea (8.2%). Adverse events classified as major and commonly considered to be related to the drug treatment were reported by two patients in the aceclofenac group (blood test: gamma-GT and SGPT increases), and 21 major adverse events were reported by nine patients in the indomethacin group (gastrointestinal tract). Study treatment was discontinued in all of these cases. The difference in the number of major adverse events was statistically significant ($P=0.032$).

Thirteen (11.9%) of the patients in the aceclofenac group and 6 (5.5%) of the patients in the indomethacin

Table 4 Adverse events with at least a possible relationship to study treatment

* WHO code

Body system	Preferred form*	Aceclofenac	Indomethacin
Non-attributed	(Blood test)	1 (0.9%)	0
Skin and appendages	Eczema	0	1 (0.9%)
	Papular rash	0	1 (0.9%)
	Pruritus	1 (0.9%)	0
	Urticaria	0	1 (0.9%)
Musculoskeletal	Arthritis	1 (0.9%)	0
	Joint inflammation	1 (0.9%)	0
	Joint pain	1 (0.9%)	0
	Muscle ache	1 (0.9%)	0
Central and peripheral nervous system	Migraine	0	1 (0.9%)
	Paraesthesia	0	1 (0.9%)
	Vertigo	3 (2.8%)	13 (11.8%)
	Concentration impairment	0	1 (0.9%)
	Neurosis	0	1 (0.9%)
Autonomic nervous system	Palpitation	1 (0.9%)	0
	Vomiting	0	1 (0.9%)
Vision	Visual disturbances	1 (0.9%)	0
Special senses: other	Taste alteration	0	1 (0.9%)
Gastrointestinal	Abdominal pain	2 (1.8%)	6 (5.5%)
	Belching	1 (0.9%)	0
	Dyspepsia	1 (0.9%)	3 (2.7%)
	Fullness, abdominal	0	1 (0.9%)
	Gastritis	2 (1.8%)	2 (1.8%)
	Heartburn	4 (3.7%)	3 (2.7%)
	Mouth dry	1 (0.9%)	0
	Nausea	0	9 (8.2%)
	Stomatitis	1 (0.9%)	0
	Vomiting	0	4 (3.6%)
Liver and biliary	Gamma-GT increased	1 (0.9%)	0
	SGPT increased	1 (0.9%)	0
Metabolic and nutritional	Weight decrease	0	1 (0.9%)
Vascular extracardiac	Vascular disorder	0	1 (0.9%)
Platelet, bleeding and clotting	Haematoma	0	1 (0.9%)
General	Chest, aching of	0	1 (0.9%)
	Epigastric pain, not food related	0	1 (0.9%)
	Facial oedema	0	1 (0.9%)
	Fatigue	1 (0.9%)	1 (0.9%)
	Head pain	0	1 (0.9%)
	Headache	0	3 (2.7%)
	Oedema, legs	0	1 (0.9%)
	Tiredness	0	2 (1.8%)
Total number of subjects		20	32
Total number of events		26	64

group showed increased laboratory test values for SGPT or SGOT after 2 and/or 12 weeks of treatment which all returned to normal after completion of the study. Six patients in the aceclofenac group and two patients in the indomethacin group already had elevated values upon admission to the study. Since many of these patients were also taking other medications, no clear connection to the study medication could be established.

Discussion

The results of this randomized, double-blind study in patients with rheumatoid arthritis indicate that the new NSAID aceclofenac is as effective as indomethacin in the symptomatic relief of pain and joint discomfort. In both treatment groups, clear and statistically significant improvement was noted for all of the clinical parameters used to characterize this disease, including the number of painful and swollen joints, duration of morning stiffness, grip strength in both hands and pain at rest. There were no sta-

tistically significant differences between the two treatments. Efficacy was also confirmed by the clinical assessment of the disease and the ARA functional classes, as well as global assessment by both the investigator and the patient.

With both drugs, symptomatic improvement was observed as early as 2 weeks into the study. In previous studies in rheumatoid arthritis, the onset of action of aceclofenac in relieving pain and joint function was shown to be faster than that of ketoprofen [10, 14] and this rapid onset appears to be a beneficial characteristic of the new NSAID. Although there were no clear differences between indomethacin and aceclofenac in continuous efficacy variables, it is worth noting that only 5.5% of aceclofenac-treated patients, as opposed to 12% on indomethacin, withdrew because of deteriorating condition.

A clear difference between the two treatments was observed in the incidence of adverse effects. Significantly more patients reported adverse events in the indomethacin ($n=42$) than in the aceclofenac group ($n=30$), and this was reflected in the number of patients in whom adverse events were considered to be possibly related to treatment (Table 4). The difference in the latter was most apparent in the incidences of gastrointestinal side effects (25.4% on indomethacin, 10.9% on aceclofenac) and CNS side effects (15.4% on indomethacin, 2.8% on aceclofenac). In fact, nine patients in the indomethacin group withdrew because of major gastrointestinal side effects, whereas in the aceclofenac group only two withdrew because of reversible increases in serum transaminases.

In a large number of clinical trials on indomethacin, the incidence of both gastrointestinal and of CNS side effects has been reported to vary between 5% and 33% [15]. Although indomethacin is commonly considered to be among the less well tolerated NSAIDs, a recent survey by the British Committee on Safety of Medicines of ten published epidemiological studies on the gastrointestinal risks associated with individual NSAIDs showed that indomethacin was consistently intermediate in the rank order of risk [16]. Moreover, a meta-analysis of 37 crossover trials comparing indomethacin with other NSAIDs indicated that indomethacin was not choosen any less than other NSAIDs [17]. The fact, then, that aceclofenac was associated with a significantly lower incidence of side effects than indomethacin and with a lower drop-out rate for lack of efficacy suggests that aceclofenac is among the best tolerated of NSAIDs for treatment of rheumatoid arthritis. This suggestion is supported by the finding in two 12-week studies in rheumatoid arthritis that aceclofenac was better tolerated than ketoprofen [12, 14]. Even in a 12-month open study in patients with both rheumatoid arthritis and osteoarthritis, aceclofenac was associated with a relatively low incidence of gastrointestinal side effects [18].

The gastrointestinal side effects of NSAIDs are the major drawback of this group of drugs for the long-term treatment of rheumatic disorders [19]. The findings that aceclofenac is just as effective as indomethacin in the relief of pain and joint dysfuncion in patients with rheumatoid arthritis, yet is associated with significantly fewer adverse events, particularly in the gastrointestinal tract, suggests that aceclofenac is an attractive, well-tolerated alternative for the treatment of rheumatoid arthritis.

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References

1. Zvaifler NL (1973) The immunopathology of joint inflammation in rheumatoid arthritis. Adv Immunol 16:256–356
2. Grau M, Guasch J, Montero JL, Felipe A, Carrasco E, Juliá S (1991) Pharmacology of the potent new non-steroidal anti-inflammatory agent aceclofenac. Arzneimittelforschung/Drug Res 41:1265–1276
3. Cecchettin M, Cerea P, Torri G (1988) Therapeutic efficacy of aceclofenac and diclofenac in acute knee arthroses. Study of the E_2-prostaglandin levels in the synovial fluid and in the serum. Clin Trials J 25:144–151
4. Díaz C, Rodríguez A, Geli C, Llobet JM, Tapounet R (1988) Comparison of aceclofenac and diclofenac in osteoarthritic pain. Curr Ther Res 44:252–256
5. Torrejón VA (1988) Treatment of severe rheumatic pain with aceclofenac: results of a comparative study vs placebo. Acta Ther 14:275–280
6. Sainz Olalla F (1989) Analgesic efficacy of aceclofenac. Double-blind study vs placebo in the treatment of odontalgia. Curr Ther Res 43:900–902
7. Bubani G (1988) The analgesic activity and tolerability of aceclofenac in the treatment of odontalgia. Clin Trials J 23: 244–253
8. Movilia PG (1988) Evaluation of analgesic activity and tolerability of aceclofenac in the treatment of postepisiotomy pain. Drugs Exp Clin Res 15:47–51
9. Ballesteros R, Ansoleaga JJ, Tapounet R (1990) The efficacy and tolerance of aceclofenac in rheumatoid arthritis. A double-blind study vs placebo. Clin Trials J 27:12–19
10. Giorgianni G, Ottaviani C, Soliano A, Campi N (1992) Efficacy and tolerability of aceclofenac versus ketoprofen in the treatment of rheumatoid arthritis. Curr Ther Res 51:175–183
11. Wassif W, Bjarnason I (1992) A comparison of the effects of aceclofenac and diclofenac on gastrointestinal blood loss. Br J Clin Res 3:109–114
12. Grupo de Estudio de Artritis Reumatoide (1992) Estudio de eficacia y tolerancia de aceclofenaco frente a ketoprofeno en el tratamiento de la artritis reumatoide. Rev Esp Reumatol 19: 263–268
13. Fehr K, Miehle W, Schattenkirchner M, Tillmann K (1989) Rheumatologie in Praxis und Klinik. Thieme, Stuttgart
14. Martín-Mola E, Gijón-Baños J (1995) Aceclofenac in comparison to ketoprofen in the treatment of rheumatoid arthritis. Rheumatol Int 15:111–116
15. Furst DE, Dromgoole SH (1987) Indomethacin and sulindac. In: Paulus HE, Furst DE, Dromgoole SH (eds) Drugs for rheumatic disease. Churchill Livingstone, New York, pp 285–314
16. Anonymous (1994) Current problems in pharmacovigilance, vol 20. U. K. Committee on Safety of Medicines
17. Gøtzsche PC (1989) Patients' preference in indomethacin trials: an overview. Lancet 1:88–91
18. Accardo S, Seriolo B, Tirri G, Colombo B, Fumagali M, Lotti G, Pagliara L, Parnham MJ, Alepuz M (1995) Long term safety profile of aceclofenac in the treatment of articular pain. Eur J Rheumatol Inflam 15:35–41
19. Lichtenstein DR, Syngal S, Wolfe MM (1995) Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. The double-edged sword. Arthritis Rheum 38:5–18