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A Randomised Double-blind Multicentre Trial Comparing Tenoxicam and Ketoprofen in Osteoarthritis †

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A double-blind multicentre study was conducted to compare the efficacy and safety of tenoxicam and ketoprofen in the treatment of osteoarthritis (OA). The study comprised 307 patients and the treatment period was 12 weeks. One-hundred and fifty-five patients received 20 mg tenoxicam once-daily and 152 patients received 100 mg ketoprofen b.i.d. Seventy-seven patients were prematurely withdrawn; 32 patients in the tenoxicam group and 45 in the ketoprofen group ($p<0.05$). There were only small insignificant differences in the efficacy parameters with the exception that significantly more patients in the tenoxicam group took paracetamol tablets during treatment. Adverse events developed in 29.0% of the patients on tenoxicam and in 47.3% of the patients on ketoprofen, this difference was statistically significant ($p<0.05$). The adverse events were predominantly from the gastrointestinal tract and the central nervous system. No serious side-effects occurred and the laboratory parameters showed no clinically relevant changes. The investigator's overall impression of treatment showed no significant difference between groups. Excellent or good results were judged in 55.2% of the patients on tenoxicam and in 62.1% on ketoprofen ($p>0.05$).

Tenoxicam appears to have a reasonable balance between efficacy and side-effects in the treatment of OA.

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INTRODUCTION

Numerous non-steroidal anti-inflammatory agents (NSAIDs) are at present available on the market worldwide. Together they consitute the most important symptomatic treatment of rheumatic disorders including osteoarthritis (OA) of the large joints (1).

Owing to the sometimes differing side-effect rates, the pharmaceutical industry is justified in continuing to search for new NSAIDs, not only with better anti-rheumatic efficacy, but also with increased tolerability.

Studies are often carried out on small numbers of patients (2,3,4), which makes it impossible to prove small, but important, differences between the drugs. Moreover, these trials are often made in hospitals on a highly selected group of patients. Furthermore, the frequency of side-effects for newly introduced products is difficult to estimate due to over-reporting of side-effects with these agents. Therefore, the aim of the present controlled multicentre study was to compare a new NSAID with a long half-life, tenoxicam, to a well known drug with a short half-life, ketoprofen, as regards efficacy as well as incidence of adverse events, in a suitable large population in general practice suffering from OA.

MATERIALS AND METHODS

The study was conducted on a multicentre basis involving 67 general practitioners and 12 rheumatologists in Denmark, between March 1987 and March 1988.

Patients aged more than 18 years with OA of the hip and/or knee and/or spine of at least six months duration were eligible for study. The diagnosis was based on the presence of moderate to severe pain at rest and on motion, or tenderness on pressure in at least one joint as observed by the investigator, and by X-ray verified evidence of OA in each affected

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joint. Excluded were pregnant and lactating women, patients with evidence of severe gastrointestinal, hepatic or renal disease, patients with previous signs of bone marrow suppression and patients with a history of hypersensitivity to NSAIDs including acetylsalicylic acid. In addition, patients who had received corticosteroids within the last six weeks and non-steroidal anti-inflammatory agents within the last week were also excluded from the study. The trial was group-comparative and in accordance with the second Declaration of Helsinki. It was approved by the regional ethical committees and the National Health Authorities and informed consent was obtained.

Patients assigned to tenoxicam took 20 mg daily as one 20 mg capsule after breakfast and one placebo capsule after supper, while those on ketoprofen took 200 mg daily as two 100 mg capsules, one after breakfast and one after supper. The treatment period was three months, and the capsules were of identical appearance. Concomitant treatment with other anti-inflammatory drugs was not allowed. Paracetamol was the only analgesic permitted and only physio and/or ergotherapy already initiated before allocation was given.

Patients were examined before allocation (baseline) and after 2, 4, 8 and 12 wecks. Intensity of pain was assessed in the same joint every time. At each visit, pain at rest and pain on motion were assessed according to a four-point ordinal scale (none, slight, moderate, severe). Functional status was also assessed on a four-point ordinal scale (unlimited normal activity, slight limitations, severe limitations, no normal activity possible). An overall judgement of efficacy and tolerance was made, independently by doctor and patient at the end of treatment according to a four-point ordinal scale (excellent, good, moderate, poor). Furthermore, the paracetamol consumption was estimated by the patient and recorded by the investigator at each control visit. Regardless of causal relationship to treatment, all adverse events were recorded at each visit and described by the investigator as to type, onset, duration, severity and outcome. Erythrocyte sedimentation rate, haemoglobin, erythrocyte, platelet and leukocyte counts, and serum alkaline phosphatase, serum aspartate aminotransferase, serum creatinine, in addition to urine analyses were determined before and after treatment.

Analyses of complaints and clinico-chemical data were based on all available patients, whilst analyses of efficacy variables were based primarily on patients who completed 12 weeks of treatment. Non-parametric data recorded during the trial was recorded using median values and range. Differences between the treatment groups for demographic data, withdrawals, adverse events and paracetamol consumption were analysed using Chi-square tests. The efficacy parameters were analysed as follows; differences between baseline and Week 12 within the treatment groups by the Wilcoxon test and differences between the two groups on each evaluation day by the Wilcoxon two-sample test. When comparing the overall judgement of treatment, again the Wilcoxon two-sample test was performed. In all cases type I error was set at 5%.

RESULTS

Three-hundred and seven patients were consecutively included in the study. One-hundred and fifty-five patients were randomised to treatment with tenoxicam and 152 to ketoprofen. Demographic data are shown in Table I. The two groups were comparable with regard to age, sex, disease duration, key joint and prior treatment. Seventy-seven patients were prematurely withdrawn, 32 patients in the tenoxicam group and 45 patients in the ketoprofen group. This difference was statistically significant ($p<0.05$). The reasons for withdrawal were either insufficient effect, side-effects or unrelated to treatment. Reasons for withdrawal are summarised in Table II.

Median and mean values for the efficacy parameters, pain at rest, pain on movement and restriction in daily activity at baseline and at each visit are shown in Table III. There was

Table I. *Demographic data*

	Tenoxicam	Ketoprofen	Both
No. of patients			
Male	51	50	101
Female	104	102	206
Age (yrs)			
Median	66	67	
Range	(50–83)	(50–89)	
Key joints (no. of patients):			
Knee	48	42	90
Hip	62	66	128
Spine	27	27	54
Other	18	17	35
Prior treatment with NSAIDs (no. of patients)	138	124	262

Table II. *Reasons for withdrawal (no. of patients and % of total material)*

		Tenoxicam		Ketoprofen
Insufficient effect		15 (9.7%)		5 (3.3%)
Side-effects:				
Gastrointestinal symptoms	11		26	
CNS symptoms	5		5	
Dermatological symptoms	1	14 (9.0%)	2	32 (21.1%)
Oedema	0		1	
Other	0		2	
Not related to therapy		3 (1.9%)		8 (5.3%)
*Total		*32 (20.6%)		*45 (29.6%)

*$p<0.05$
Note: one patient can have more than one side-effect.

Table III. *Efficacy: median (mean) values of clinical parameters by treatment and times.*

	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Pain at rest:					
Tenoxicam	1 (1.35)	1 (0.96)	1 (0.80)	1 (0.68)	1 (0.72)
Ketoprofen	1 (1.38)	1 (0.94)	1 (0.76)	1 (0.73)	1 (0.68)
Pain on movement:					
Tenoxicam	2 (2.30)	2 (1.66)	1 (1.42)	1 (1.31)	1 (1.39)
Ketoprofen	2 (2.24)	2 (1.67)	1 (1.44)	1 (1.44)	1 (1.28)
Degree of restriction in daily activity:					
Tenoxicam	1 (1.27)	1 (1.05)	1 (0.91)	1 (0.96)	1 (0.93)
Ketoprofen	1 (1.26)	1 (1.01)	1 (0.99)	1 (0.99)	1 (0.89)

No significant differences between groups.

Table IV. *Type of complaints by patients and % of total material*

No. of patients with at least one AE	Tenoxicam (n=155)		Ketoprofen (n=158)	
Gastrointestinal tract				
Epigastric pain	17		24	
Nausea	6		23	
Vomiting	0	n = 26 (16.8%)	3	n = 55 (36.7%)
Diarrhoea	3		5	
Constipation	6		11	
Dyspepsia	6		20	
Central nervous system				
Dizziness	11		5	
Headache	1		2	
Vertigo	2	n = 10 (6.4%)	0	n = 6 (4.0%)
Tiredness	2		1	
Depression	0		1	
Other complaints				
Itching	3		0	
Exanthema	1		2	
Oedema	2	n = 9 (5.8%)	4	n = 10 (6.6%)
Palpitations	2		1	
*Total	*45 (29.0%)		*71 (47.3%)	

*$p<0.05$
Note: one patient can have more than one adverse event.

Table V. *Overall judgement on treatment*

	Tenoxicam (n=114)	Ketoprofen (n=116)
Investigator's judgement		
Excellent	20 (17.5%)	17 (14.7%)
Good	43 (37.7%)	55 (47.4%)
Moderate	37 (32.5%)	27 (23.3%)
Poor	14 (12.3%)	17 (14.6%)
Patient's judgement		
Excellent	23 (20.2%)	18 (15.5%)
Good	36 (31.6%)	52 (44.8%)
Moderate	33 (28.9%)	22 (19.0%)
Poor	22 (19.3%)	24 (20.7%)

No significant differences between groups.

no significant difference at baseline among the groups and significant improvement from baseline to Week 12 for all three parameters could be seen in both groups. Differences between groups were never statistically significant ($p<0.05$). A summary of adverse events (AE) and their probable or possible relation to treatment are presented in Table IV. Twenty-nine per cent of the tenoxicam treated patients experienced at least one adverse event compared to 47.3% of those treated with ketoprofen ($p<0.05$).

The adverse events were predominantly from the gastrointestinal tract and the central nervous system. No cases of haemorrhage, ulcerous perforation or other serious side-effects occurred. The types of complaints by number of patients are also shown in Table IV. No clinically relevant changes occurred in the laboratory parameters in either group. The

investigator and patient impression at the conclusion of the study did not show any statistically significant differences between the drugs (Table V). The investigator's judgement showed excellent or good results in 55.2% of the patients on tenoxicam and in 62.1% on ketoprofen ($p>0.05$).

DISCUSSION

This study was designed in order to obtain a reliable impression of efficacy and adverse events of a newly introduced NSAID compared to a well-known drug. The investigation was conducted as a multicentre trial in general practice and the recommended doses of the two drugs were used in order to reflect the usual clinical practice as closely as possible.

In this study, most of the patients had beneficial effects from both drugs and there was no significant difference between the two drugs regarding the efficacy and overall judgement. The finding that significantly more patients in the tenoxicam group took paracetamol tablets, may be due to the possibility that the recommended doses are not quite equipotential concerning pain relief. This explanation is supported when looking at the reasons for the patients to withdraw from treatment. Lack of efficacy was the cause for withdrawal in 9.7% of the patients in the tenoxicam group, and 3.3% in the ketoprofen group. Another possible explanation might be that the paracetamol consumption was based on the patients own estimation, which might be unreliable.

On the other hand, we found that 9.0% of the patients in the tenoxicam group withdrew because of side-effects compared to 21.1% on ketoprofen. This difference in tolerability is also reflected in the total incidence of adverse events as 29.0% of the patients on tenoxicam and 47.3% on ketoprofen experienced at least one adverse event during treatment. These differences are highly significant.

A previous study by Kirchheiner *et al.* (5), compared the efficacy and tolerance of 20, 30 and 40 mg tenoxicam given once-daily and indomethacin 25 mg t.i.d. in 77 patients with OA. As regards efficacy, they found that patients on higher doses of tenoxicam usually fared slightly better, but dose-effect relations were always insignificant. Similarly, no statistically significant differences between the groups were observed as regards side-effects, but the trend was in favour of patients on 20 mg tenoxicam.

A high incidence of adverse events has previously been demonstrated in a multicentre study by Husby *et al.* (6). This study comprised 2,035 patients with OA treated with either piroxicam or naproxen and the total incidence of adverse events observed was 43.3% and 45.6%, respectively. These figures seem quite high, compared to those reported in previous studies (7). However, in contrast, both studies were conducted in general practice among a heterogenous group of daily users of NSAIDs.

Taking both efficacy and tolerance into consideration, this study revealed the problem of finding a reasonable balance between efficacy and side-effects. The study indicated that a small gain in efficacy may result in an unacceptable increase in the number of side-effects.

CONCLUSION

Excepting the uncertainty concerning the paracetamol consumption, the two drugs seem to be identical with regard to efficacy for all practical purposes. As regards tolerance, significantly more adverse events developed in patients treated with ketoprofen. In conclusion, tenoxicam seems to have a favorable balance between efficacy and side-effects in the treatment of OA.

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