

Comparison of Therapeutic Efficacy of Nimesulide and Diclofenac in Patients with Degenerative Joint Diseases

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The efficacy and tolerability profiles of nimesulide and diclofenac were evaluated in 180 patients suffering from various degenerative joint diseases. The clinical evaluations were performed at 0, 2 and 4 weeks. Nimesulide (100 mg) tablets were administered twice daily and diclofenac (50 mg) tablets were administered thrice daily. The principal efficacy parameters were the improvement in pain assessed through verbal scoring. Evaluation of tolerance was also established through similar method. Final judgment on efficacy was made by the physician. In all evaluations nimesulide showed improved efficacy parameters over diclofenac.

Pharmacotherapy of rheumatic diseases has significantly improved over the last two decades with the advent of new non-steroidal anti-inflammatory drugs (NSAIDs). Among the recent marketed NSAIDs which are clinically used, nimesulide (4-nitro-2-phenoxy methyl sulphonanilide) has proved effective therapeutics. Its success is attributed to its adequate safety profile. Since nimesulide more selectively inhibits pathologically induced cyclooxygenase-2 (COX-2) at the time of inflammation¹ and not cyclooxygenase-1 (COX-1) present in the gut mucosa or other physiological sites, its tolerability profile is expected to be much better than many other conventional NSAIDs. Several studies^{2,3} on the efficacy of nimesulide in joint and sports injuries, osteo-arthritis, osteo-arthrosis of knee and hip and other important degenerative joint diseases have been published. We think that the incidence of nimesulide adverse effects on the gastro-intestinal tract will be significantly low in comparison with other NSAIDs since it selectively inhibits prostaglandin synthesis induced by COX-2. Therefore, our purpose of conducting this randomised double blind study was to establish a comparative clinical profile of therapeutic efficacy and tolerability of nimesulide *versus* diclofenac sodium.

MATERIAL AND METHOD

One hundred and eighty outpatients with osteo-arthrosis of hip, knee and lumbar spine of both sexes aged between 18-80 years [Tables 1&2] were enrolled at Military Medical Academy (MMA), Belgrade and Faculty of Medicine, University of Prishtina. Nimesulide (Nimulid O, Panacea Biotec) 200 mg divided in two equal daily doses was compared with diclofenac sodium (Panfarm, Belgrade) 150 mg in three equally divided daily doses. Patients were included in the study in order of their visit to the rheumatologist and randomly assigned into one of the groups. Patients enrolled had moderate to marked evident symptoms of osteo-arthritis so that, the long-term therapy with NSAIDs was necessary.

Scale of evaluation —

Each patient included in the study was interviewed three times: on day '0' (zero) and

Sex	Nimesulide			Diclofenac		
	MMA	Prishtina	Total	MMA	Prishtina	Total
Male	22 (44%)	12 (30%)	34 (38%)	28 (56%)	16 (40%)	44 (49%)
Female	28 (56%)	28 (70%)	56 (62%)	22 (44%)	24 (60%)	46 (51%)
Total	50 (100%)	40 (100%)	90 (100%)	50 (100%)	40 (100%)	90 (100%)

Localisation	Nimesulide			Diclofenac		
	MMA	Prishtina	Total	MMA	Prishtina	Total
Spine	12 (24%)	8 (20%)	20 (22%)	5 (10%)	27 (68%)	32 (36%)
Knee	15 (30%)	23 (58%)	38 (42%)	33 (66%)	7 (17%)	40 (44%)
Hip	23 (46%)	9 (22%)	32 (36%)	12 (24%)	6 (15%)	18 (20%)
Total	50 (100%)	40 (100%)	90 (100%)	50 (100%)	40 (100%)	90 (100%)

subsequently after 2 and 4 weeks. Within this 4-week period patients were every day given either nimesulide or diclofenac. On first examination severity of osteo-arthrosis was evaluated using a three degree scale (1-mild, 2-moderate, 3-severe) and at each next visit patients were asked to evaluate momentary intensity or change in the symptom intensity of osteo-arthrosis using a five degree scale (1-worse than before, 0-as before, 1 (a)- little better than before, 2-markedly better than before, 3-significant improvement). As an additional parameter patients subjective evaluation of pain intensity was also recorded in special list containing 4 degree scale (0-no pain, 1-pain of mild intensity, 2-moderately severe pain, 3-very severe pain) as well as degree of pain relief and examiner's evaluation of drug effect using a 4 degree scale (3-poor/ no effect, 2-good/partially relieved pain, 1-very good/significantly relieved pain, 0-excellent / completely relieved pain).

Evaluation of drug tolerance was made after 2 and 4 weeks by recording adverse effects intensity in 5 degree scale (0-no effect, 1-mild and transient, not requiring drug therapy, 2-moderate, constant, but administration of the studied drug was continued due to its therapeutic effects together with symptomatic therapy which was recorded in a list afterwards, 3-marked, unbearable so that the patient discontinued its usage, 4-very marked, life threatening and requiring therapy discontinuation and hospitalisations). Additionally blood samples for routine haematology and biochemical analysis were taken at the beginning of the study as well as after 2 and 4 weeks. Finally overall tolerance of the examined drugs was reported on a 4-degree scale (0-poor, 1-good, 2-very good, 3-excellent).

OBSERVATIONS AND DISCUSSION

As seen from Table 3 two groups of patients had similar degree of osteo-arthritis symptoms before examination suggesting a justifiable comparison. A statistically significant ($p < 0.05$) faster improvement was observed with nimesulide than diclofenac. After 2 weeks nimesulide therapy indicated "evidently better" response and after 4 weeks indicated "significant improvement" while the ones on diclofenac therapy described their condition in the same interval as "a little better than before" and then "evidently better".

Initial reduction in pain score was 38% for nimesulide and 36% for diclofenac at two weeks. After 4 weeks of the therapy, nimesulide showed significantly marked reduction of this score (86%) than diclofenac (54%) when scoring according to initial value (Fig 1). Pain relief in patients treated with nimesulide was also described as "very good (significantly relieved pain)" after 2 weeks and as "excellent (completely relieved pain)" after 4 weeks. Diclofenac in the same intervals exhibited effects described as "good (partially relieved pain)" with tendency to reach "very good (significantly reduced pain)" but not until the end of the study.

Evaluation of tolerance for both of these drugs was made after 2 and 4 weeks on the basis of detailed history of the disease and finally through asking routine question "Did you experience any unpleasant sensation during the last two weeks?". If the answer was positive, the patient was asked to evaluate degree of that adverse effect and derive a final evaluation of the drug tolerance. These results are shown in Table 4. It suggests that the score of adverse effects in both therapeutic groups increase with therapy between 2 to 4 weeks and the absolute value is 2-3 times higher in patients treated with diclofenac than nimesulide. Both examiners and patients evaluated general nimesulide tolerance as "excellent" while the score of diclofenac was "very good".

Table 3—Evaluation of the Effects of Nimesulide and Diclofenac in the Treatment of Osteo-arthrosis of the Hip, Knee and Lumber Spine

Parameter	Nimesulide			Diclofenac		
	MMA	Prishtina	Total	MMA	Prishtina	Total
Severity of disease (mean \pm SE):	2.4 \pm 0.1	2.3 \pm 0.1	2.4 \pm 0.2	2.1 \pm 0.1	2.1 \pm 0.1	2.1 \pm 0.1
Change in condition after 2 weeks	2.0 \pm 0.1	2.0 \pm 0.1	2.0 \pm 0.1	1.5 \pm 0.1	1.1 \pm 0.2	1.3 \pm 0.1
Change in condition after 4 weeks	3.0 \pm 0.1	2.5 \pm 0.2	2.8 \pm 0.1	2.4 \pm 0.2	1.3 \pm 0.3	1.9 \pm 0.2
Subjective evaluation of pain intensity:						
Initial pain intensity	3.0 \pm 0.1	2.8 \pm 0.1	2.9 \pm 0.1	2.8 \pm 0.1	2.9 \pm 0.1	2.8 \pm 0.1
Pain intensity after 2 weeks	1.9 \pm 0.1	1.6 \pm 0.1	1.8 \pm 0.1	1.8 \pm 0.1	1.7 \pm 0.2	1.8 \pm 0.1
Pain intensity after 4 weeks	0	0.9 \pm 0.2	0.4 \pm 0.1	0.9 \pm 0.2	1.8 \pm 0.2	1.3 \pm 0.2
Pain relieved after 2 weeks	1.0 \pm 0.1	1.5 \pm 0.1	1,2 \pm 0.1	1.7 \pm 0.1	2.1 \pm 0.2	1.9 \pm 0.1
Pain relieved after 4 weeks	0	0.7 \pm 0.2	0.3 \pm 0.1	1.1 \pm 0.2	2.1 \pm 0.2	1.5 \pm 0.2

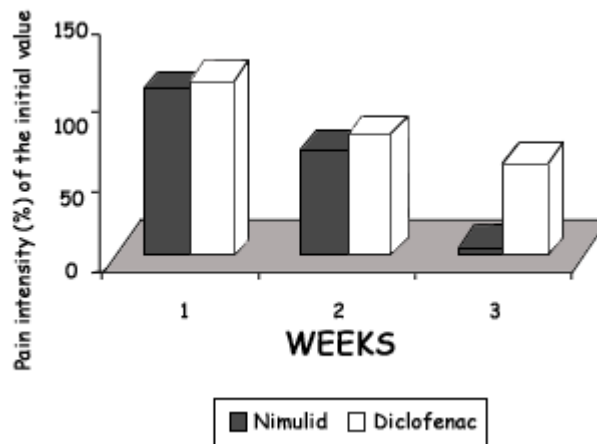
Physician's evaluation after 2 weeks	1.0±0.1	1.5±0.1	1.2±0.1	1.6±0.1	2.1±0.3	1.8±0.2
Physician's evaluation after 4 weeks	0	0.7±0.2	0.3±0.1	1.0±0.2	2.1±0.3	1.5±0.2

Among all adverse effects of both drugs gastro-intestinal symptoms such as nausea, epigastric burning and vomiting were predominant and significantly frequent in patients receiving diclofenac (Table 5). Total values, thus, show that every third patient receiving this therapy suffer from some adverse effect in comparison with every eighth patient receiving nimesulide. One patient from each group was excluded from the study after 2 weeks due to marked gastric drug intolerance. Results of the laboratory analysis of haematological and biochemical parameters of all patients were similar in both groups.

Table 4—Evaluation of Nimesulide and Diclofenac Tablets Tolerance in the Treatment of Osteoarthritis of the Hip, Knee and Lumbar Spine (P<0.05)

Parameter	Nimesulide			Diclofenac		
	MMA	Prishtina	Total	MMA	Prishtina	Total
Intensity of adverse effects after 2 weeks (mean±SE)	0.1	0	0.1±0.1	0.2±0.1	0.4±0.2	0.3±0.1
Intensity of adverse effects after 4 weeks (mean±SE)	0.2	0	0.2±0.1	0.2±0.1	0.7±0.3	0.4±0.2
Physician's evaluation of tolerance	3.0±0.1	3.0±0.1	3.0±0.1	2.4±0.2	1.3±0.3	1.9±0.2
Patients evaluation of tolerance	3.0±0.1	2.9±0.1	3.0±0.1	2.7±0.1	1.2±0.1	2.0±0.1

Figure 1: Effect of nimesulide and diclofenac therapy upon pain intensity in patients with osteoarthritis of the hip, knee and lumbar spine



Controlled clinical trials have shown significant therapeutic effect of nimesulide in rheumatic pains in 80-90% of patients. Analgesia with nimesulide has been found to be effective in pain associated with rheumatoid arthritis, osteo-arthritis, juvenile chronic arthritis, degenerative rheumatism and other related painful disorders^{2,4}. Several studies have demonstrated its superior anti-inflammatory and analgesic effect and tolerability in comparison with diclofenac^{5,6}. In comparison with other NSAIDs, therapy with nimesulide is associated with lesser adverse effects as it is

differentially selective to inhibition of pathologically induced cyclooxygenase-2 (COX-2) at inflammation site and less active against constitutive cyclooxygenase-1 (COX-1) of kidney, stomach, and lung necessary for physiologic role of prostaglandin in human body⁷. This comparative clinical trial of analgesic effects of nimesulide and diclofenac in 180 patients with osteoarthritis of the hip, knee and lumbar spine confirmed that both drugs' were efficacious while nimesulide exerted much better tolerability profile.

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Adverse effect	Nimesulide	Diclofenac
Nausea	4 (4.44%)	15 (29.99%)
Gastric irritation	2 (2.22%)	9 (10.00%)
Vomiting	0 (0%)	4 (4.44%)

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