doi: 10.1111/j.1742-1241.2007.01453.x

ORIGINAL PAPER

International Journal of Clinical Practice

Effects of nimesulide on pain and on synovial fluid concentrations of substance P, interleukin-6 and interleukin-8 in patients with knee osteoarthritis: comparison with celecoxib

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Disclosures
The authors declared that they had no interests which might be perceived as posing a conflict or bias.

SUMMARY

Objective: This study was designed to investigate the analgesic effects of nimesulide and celecoxib in patients with knee osteoarthritis (OA). In patients with joint effusion, the effects of these non-steroidal anti-inflammatory drugs (NSAIDs) on synovial fluid concentrations of substance P (SP), interleukin (IL)-6 and IL-8 also were evaluated. **Methods:** Patients were randomly assigned either nimesulide (100 mg twice a day) or celecoxib (200 mg once a day) for 2 weeks. The intensity of joint pain was assessed with a 100-mm visual analogue scale (VAS). Furthermore, patients completed questions about analgesic efficacy and overall tolerability of the treatments on a five-point categorial scale. Synovial fluid samples were drawn at baseline, 30 min after the first drug intake (day 1), and 30 min after the last drug intake (day 14). **Results:** We enrolled 44 patients, 20 of whom had a joint effusion. In this group, the effects of nimesulide were more marked than for celecoxib, with evidence of a faster onset of the analgesic action. Both after a single or repeated administration, nimesulide significantly reduced the synovial fluid concentrations of SP and IL-6. Celecoxib, on the other hand, did not change the concentrations of SP and significantly reduced the levels of IL-6 only on day 14. None of the drugs affected IL-8. Both drugs were generally well tolerated. **Conclusions:** These results provide evidence that nimesulide is an effective agent for the symptomatic treatment of OA. The effect on inflammatory pain mediators is consistent with the fast analgesic action of this NSAID.

What's known
A number of studies have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs), including nimesulide and celecoxib, are effective in the symptomatic treatment of osteoarthritis (OA). Substance P (SP), interleukin (IL)-6 and IL-8 have been associated with OA inflammation and pain. It has been demonstrated that nimesulide has the advantage of a rapid onset of the analgesic effect on patients with knee OA.

What's new
In OA patients with joint effusion, the synovial fluid concentrations of substance P and IL-6 were reduced after a single or repeated administration of nimesulide. Celecoxib did not change the concentrations of SP and significantly reduced the levels of IL-6 only after the repeated administration. SP may be involved in nimesulide-induced analgesia. The effect on these inflammatory pain mediators is consistent with the fast analgesic action of nimesulide in OA patients. To the best of our knowledge, this study is the first to evaluate the synovial fluid concentration of these inflammatory pain mediators after administering nimesulide and celecoxib.

Osteoarthritis (OA) is one of the most common forms of musculo-skeletal disease that affects millions of people worldwide (1–3). The most prominent symptom of OA is pain. The severity of pain often prompts treatment with non-steroidal anti-inflammatory drugs (NSAIDs), which are the preferred analgesics by many patients with OA (4,5). A number of NSAIDs are available for the therapy in OA patients, and many clinicians prefer these drugs to simple analgesics, such as paracetamol (6). Moreover, there is a commonly held belief that patients with inflammatory OA (characterised by the presence of joint effusion) may be particularly responsive to NSAIDs, although these compounds may show different analgesic properties (7,8).

Nimesulide is an NSAID with unique chemical features belonging to the sulphonanilide class, with a preferential inhibition on cyclooxygenase (COX)-2 activity and less effect on COX-1 (9). A considerable number of studies have demonstrated that nimesulide is an effective drug for the symptomatic treatment of OA, with a convenient dosing schedule of 100 mg twice a day (10). Celecoxib is a sulphonamide belonging to the group of COX-2 selective inhibitors (11). In clinical trials, celecoxib 200 mg was found to reduce the signs and symptoms of OA (12–14). With reference to selectivity for COX-2, nimesulide and celecoxib may be classified in the group of NSAIDs showing a five to 50-fold selectivity for COX-2 over COX-1 (11,15). However, they

display different chemical, pharmacokinetic and pharmacodynamic characteristics. In particular, nimesulide has an anti-inflammatory and analgesic activity that goes beyond the COX inhibition, and involves a wide range of inflammatory and pain mediators (9,16).

Osteoarthritis pain is an example of a complex type of pain that involves multiple structures and mediators (17,18). The joint is innervated by different types of small-diameter sensory nerve fibres, whose endings (nociceptors) are responsible for pain transmission (19,20); many of these fibres contain neuropeptides, such as substance P (SP). It has been demonstrated that fibres containing SP are present in most joint structures, including the periosteum, the subchondral bone and the capsule (21,22); excitation of these nerve fibres by mechanical, thermal and chemical painful stimuli leads to an antidromic release of SP into the joint. This process, called neurogenic inflammation, may contribute to amplify OA pain (23–26).

Although the causes of OA are not completely understood, biochemical changes in the subchondral bone, articular cartilage and synovial membrane are important in its pathogenesis (3–27). In OA, it has been demonstrated that osteoblasts, chondrocytes and inflamed synovium produce several pro-inflammatory cytokines and chemokines (28–31). Among these, interleukin (IL)-6 and IL-8 have been shown to be associated with inflammation and to be involved in the cartilage degradation process in OA (28,32,33).

In view of above-mentioned reasons, we considered it of interest to compare the effects produced by nimesulide and celecoxib on joint pain and on synovial fluid concentrations of SP, IL-6 and IL-8 in patients with knee OA. As it has been demonstrated that nimesulide has the advantage of a rapid onset of the analgesic effect (34,35), in this study we paid special attention to the effects induced by drugs at short time (i.e. 30 min) after their administration. To the best of our knowledge, our present study is the first of its kind to evaluate the synovial fluid levels of inflammatory pain mediators after administering nimesulide and celecoxib.

Study population and methods

Study population

Men and women outpatients aged 18 years or older were eligible to participate in the study if they fulfilled the American College of Rheumatology criteria for a diagnosis of OA (36). Patients had both clinical (knee pain for at least 1 month, morning stiffness lasting 30 min or less, and crepitus on motion) and radiographic evidence of knee OA. Radiographic criteria were joint-space narrowing with the presence of osteophytes. The severity of joint destruction was judged similar in all the enrolled patients (grade 2 or 3, according to the Kellgren and Lawrence classification scale) by the main investigator expert in rheumatology.

The knee designed as the 'study joint' was the main source of pain in the lower extremity. Inclusion criteria also had a minimum visual analogue scale (VAS) score of 40 mm for the basal assessment of pain connected with walking. Any treatment with NSAIDs or other analgesics was discontinued at least 72 h before the study. Patients were excluded if they had a concurrent arthritic disease, such as chronic inflammatory arthritis, including rheumatoid arthritis, gout or pseudogout, values of laboratory resulted outside normal reference range (calculated creatinine clearance < 30 ml/min, plasma alanine aminotransferase and aspartate aminotransferase > 40 U/l), or a history of allergy to study drugs or hypersensitivity to nimesulide, celecoxib or any other NSAID. The presence of non-degenerative joint diseases (e.g. infectious and microcrystalline) or eligibility for surgical intervention represented exclusion criteria. Following an explanation of the nature of the study, each patient gave his written informed consent to the study.

Study design

This was a prospective, randomised, double-blind, between-patient study comparing two NSAIDs at indicated doses for the symptomatic treatment of knee OA, over 2 weeks. The primary efficacy endpoint was the intensity of joint pain during walking measured with a 100-mm VAS.

Enrolled patients were assigned by computer-generated random numbers to treatment with nimesulide 100 mg p.o. twice a day or celecoxib 200 mg p.o. once a day. During the study all the patients suspended any other analgesic intake. Investigators and patients remained blinded to individual patient allocation throughout the study. To guarantee the blind conditions each patient was given an identical sachet and told that if he or she found 14 tablets of the drug, the dosage was one tablet a day, whereas if the sachet contained 28 tablets, the dosage was two tablets a day. Afterwards, the collection of data on the intensity of pain was performed by a clinician (PB) who was unaware of the experimental protocol. Data regarding the efficacy of the treatments were collected prior to the first drug administration, and on the first (day 1) and the last day (day 14) of each drug treatment. The trial was conducted in the Rheumatology Unit of the Ospedale di Circolo e Fondazione Macchi, Varese (Italy) in accordance

with the principles of good clinical practice and the Declaration of Helsinki. Approval for this study protocol was given by the Ethics Committee of the Ospedale di Circolo e Fondazione Macchi. The trial is registered as N. 465.

Assessment of the analgesic efficacy

The main efficacy criterion was the assessment of the intensity of pain by using the VAS measured on a scale of 0–100 mm. The VAS consisted of a 100 mm line with the end-points 'no pain' and 'worst pain'. On day 1 and on day 14 patients recorded their intensity of pain before consuming the medicine and 30 min after its intake. All VAS scores were measured during walking. The patients were asked to make a mark on the line that represented their current pain intensity, and the pain intensity score was defined by measuring the distance from the 'no pain' end of the line in mm. Moreover, at the end of the study period, patients also completed questions about the analgesic efficacy on a five-point categorial scale: none, mild, moderate, good and very good.

Tolerance assessment

At the end of the period of treatment (14 days) patients completed questions about the overall tolerance of the treatment on a five-point categorial scale: very poor, poor, fair, good and excellent.

Collection of synovial fluid

The presence of joint effusion was clinically ascertained by the manual manoeuvring of the patella, and the appreciation of the bulge sign. Synovial fluid samples were obtained at baseline and 30 min after drug intake both after the first dose (day 1) and the last dose (day 14). Freshly aspirated synovial fluid (3.0 ml) was collected in tubes containing ethylenediaminotetraacetic acid (EDTA). The fluid was centrifuged for 10 min at $1500 \times g$ at 4 °C, the supernatant collected and frozen at −20 °C until assay.

Measurement of synovial fluid concentrations of SP, IL-6 and IL-8

Substance P was measured by radioimmunoassay (RIA), using antiserum and methods previously described and validated (37).The antibody was raised in rabbit against synthetic SP, and it is directed towards the C-terminal of the peptide; ^{125}I-SP was purchased from Amersham Bioscience (Milan, Italy). Sensitivity of the RIA is 10 pg/tube and intrassay and interassay variation coefficients are 8% and 11% respectively.

The levels of IL-6 and IL-8 were determined by enzyme-linked immunosorbent assay by the mean of commercially available kits (BD OptEIA) for human IL-6 and IL-8 (BD Biosciences, San Diego, CA). Sensitivity of the method for IL-6 and IL-8 quantification was indicated in 2.2 and 0.8 pg/ml respectively. All the samples were evaluated by an operator who was unaware of the experimental design.

Statistical analysis

Sample size determination was performed by a nomogram for calculating sample size for studies using continuous variables, on the basis of our preliminary observations on patients with OA pain (35,38), and assuming an alpha error of 0.05 and beta error of 0.20. The primary outcome for power calculation was the intensity of pain measured with a 100-mm VAS. It was estimated that a difference of 10 mm between the VAS measured 30 min after drug intake and that measured at baseline on day 1, with a standard deviation of ±8, could be considered clinically significant. On the basis of this estimation, the number of 10 patients in each treatment group represented the minimum number required for the analysis. As our stratified groups of patients (with or without effusion) included 20 and 24 subjects, respectively, this study was expected to show statistical differences between the reduction in the intensity of pain induced by the administration of drug in the two subsets of patients. In fact, data regarding at least 10 patients treated with nimesulide or celecoxib were always available even after stratification on the basis of presence/absence of joint effusion. With regard to the effects on the synovial fluid concentrations of SP, IL-6 and IL-8, it was more difficult to define a clinically significant reduction and, therefore, to conduct a power calculation. For this reason, these results could be labelled as 'exploratory'.

The comparison between the VAS scores at each point in time following the administration of the drug and those measured at baseline was performed by one-way ANOVA for repeated measures followed by Tukey's test. The same test was used to analyse the results regarding SP and IL concentrations in the synovial fluid. The data regarding the changes in pain intensity in the two groups of treatment were compared by using one-way ANOVA. The changes in the intensity of pain were correlated to the reduction of synovial fluid SP and IL-6 by means of Pearson's correlation test. For all comparisons, differences were considered significant at $p < 0.05$.

Results

Between September 2004 and November 2005, we enrolled 44 patients (6 men and 38 women), 24 of whom had a painful knee joint without synovial fluid effusion, while 20 had a painful knee joint with synovial fluid effusion. Consecutive patients fulfilling

inclusion criteria were recruited. All the enrolled patients completed the study. The mean age was 71.0 ± 1.1, with an age range from 49 to 81 years. The characteristics of the patients who entered the study are summarised in Table 1.

In the light of the mean age of the patients, the present study may be considered a study of the elderly patients. There were no significant differences between the groups with respect to age, sex and clinical condition. The two groups were comparable if we consider the intensity of pain at baseline. Indeed, no statistically significant difference was observed in the VAS scores obtained in the two groups of patients before the first drug administration (Figure 1 and Table 2). Before treatment, all the patients recorded a score of more than 40, indicating that the patient would have recorded at least moderate pain on a four-point (none, mild, moderate and severe) categorial scale (39).

Change in pain intensity – day 1

In patients with synovial fluid effusion, the analgesic effect of nimesulide was more marked than for celecoxib. Indeed, in the group of patients treated with nimesulide, the VAS scores measured 30 min after the intake of the drug were significantly lower than those measured in basal conditions (Figure 1), whereas this difference was not statistically significant in patients treated with celecoxib. Consistent with this observation, the relief of pain as measured by pain intensity difference (PID) was significantly greater for nimesulide than for celecoxib (Figure 2). On the other hand, both treatments were similarly effective on patients not having synovial fluid effusion (Table 2). It is important to add that the pain relief measured as PID was significantly greater for nimesulide than for celecoxib also when the effects of these two drugs were evaluated in each treatment group as a whole (patients with joint effusion plus patients without joint effusion). In fact, the PID in nimesulide group ($n = 22$) resulted of 18.2 ± 2.0, and the PID in celecoxib group ($n = 22$) resulted of 11.3 ± 1.7 [F (1,43) = 6.5, p = 0.014].

Table 1 Characteristics of the patients who entered the study

	Nimesulide	Celecoxib
Age (years, mean ± SEM)	70.8 ± 1.8	71.3 ± 1.4
Female	20	18
Male	2	4
With SF effusion	10 (9 F, 1 M)	10 (8 F, 2 M)
Without SF effusion	12 (11 F, 1 M)	12 (10 F, 2 M)

SF, synovial fluid.

Change in pain intensity – day 14

On the morning of the last day of treatment, the intensity of pain measured in the two groups of patients before the intake of drug was significantly lower than that measured in basal conditions on day 1. This reduction in the intensity of pain before the intake of drug was evident both in patients with synovial fluid effusion and in patients without joint effusion (Figure 1 and Table 2). Following the administration of nimesulide, VAS scores measured 30 min after the intake of drug were significantly lower than those measured before it (Figure 1 and Table 2), whereas no statistically significant reduction of pain was seen in patients treated with celecoxib. Accordingly, the relief of pain assessed by PID in patients with joint effusion was significantly greater for nimesulide than for celecoxib (Figure 2). The

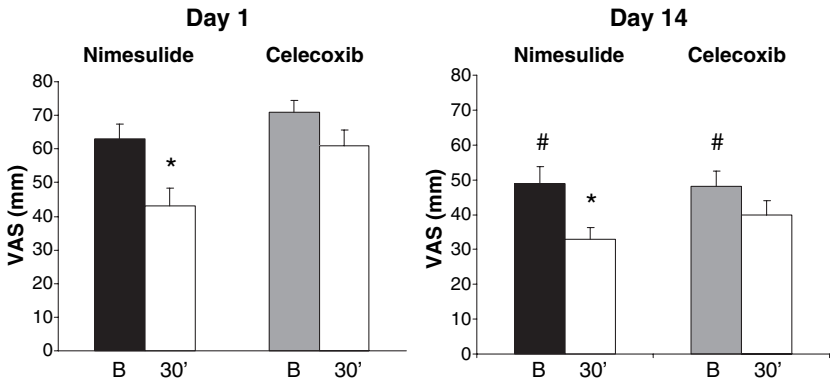

Figure 1 Pain intensity as recorded by patients with knee osteoarthritis associated with joint effusion on a 100 mm visual analogue scale (VAS) at baseline (B) and at 30 min after drug administration on the first day (day 1, left panel) and on the last day (day 14, right panel) of treatment with nimesulide or celecoxib. *p < 0.05 vs. baseline (B); #p < 0.05 vs. baseline on day 1

Table 2 Pain intensity as recorded by patients with knee osteoarthritis without joint effusion on a 100 mm visual analogue scale before and 30 min after drug administration at day 1 and at day 14 following treatment with nimesulide or celecoxib

Treatment	Baseline	T30	PID
Day 1			
Nimesulide (n = 12)	67.8 ± 3.9	50 ± 5.0*	17.5 ± 2.9
Celecoxib (n = 12)	62.0 ± 3.0	49 ± 3.7*	12.7 ± 2.4
Day 14			
Nimesulide (n = 12)	53.0 ± 2.4#	42 ± 2.9*	11.0 ± 2.4
Celecoxib (n = 12)	50.0 ± 3.7#	41 ± 3.3	10.1 ± 1.9

Values are means ± SEM. *p < 0.05 vs. baseline. #p < 0.05 vs. baseline at day 1. PID, pain intensity difference.

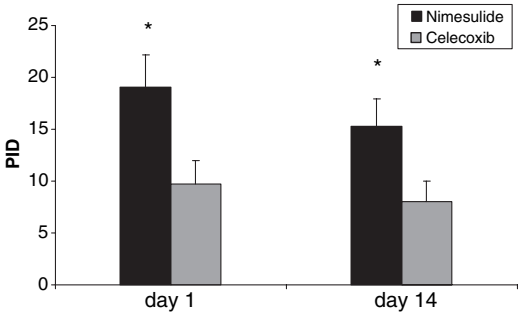

Figure 2 Pain relief, expressed as pain intensity differences (PID), produced by nimesulide and celecoxib in patients with osteoarthritis and synovial fluid effusion. *p < 0.05 vs. celecoxib

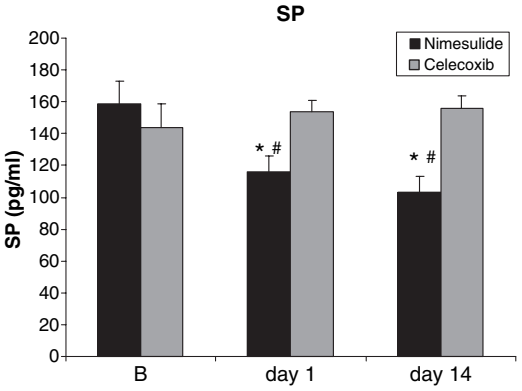

Figure 3 Synovial fluid concentrations of substance P (SP) measured in patients with knee osteoarthritis associated with joint effusion 30 min after drug administration on the first day (day 1) and on the last day (day 14) of treatment with nimesulide or celecoxib. *p < 0.05 vs. baseline (B); #p < 0.05 vs. celecoxib

relief of pain measured as PID was more evident for nimesulide than for celecoxib also when the effects of these two drugs have been evaluated in each treatment group as a whole (patients with joint effusion plus patients without joint effusion). In fact, the PID in nimesulide group ($n = 22$) resulted of 13.7 ± 1.7, and the PID in celecoxib group ($n = 22$) resulted of 9.1 ± 1.3 [F (1,43) = 4.2, p = 0.046].

Change in synovial fluid SP concentrations

The data on the measurement of synovial fluid SP are shown in Figure 3. Both on day 1 and on day 14, the synovial fluid concentrations of SP were significantly reduced by the treatment with nimesulide. Indeed, the statistical analysis showed that the values obtained in this group of patients following the administration of drug were significantly lower than those measured at baseline (basal = 159 ± 14; post-treatment on day 1 = 116 ± 10; post-treatment on day 14 = 103 ± 10, pg/ml, means ± SEM). In contrast, no significant changes in SP concentrations were induced by the treatment with celecoxib (basal = 144 ± 15; post-treatment on day 1 = 154 ± 7.0; post-treatment on day 14 = 156 ± 8.0). From a statistical point of view, the reduction in the synovial fluid concentrations of SP did not correlate with the reduction in the intensity of pain.

Change in synovial fluid IL-6 concentrations

The data on the measurement of synovial fluid IL-6 are shown in Figure 4. Both on day 1 and on day 14 the treatment with nimesulide produced a significant reduction in the synovial fluid concentrations of this cytokine. Indeed, the statistical analysis showed that the values obtained following the administration of the drug were significantly lower than those measured at baseline (basal = 390 ± 44; post-treatment on day 1 = 306 ± 33; post-treatment on day 14 = 255 ± 31, pg/ml). In contrast, in the group of patients treated with celecoxib, the IL-6 concentrations were significantly reduced compared with basal values only on day 14 (basal = 354 ± 32; post-treatment on day 1 = 308 ± 23; post-treatment on day 14 = 212 ± 21, pg/ml). From a statistical point of view, the reduction in the synovial fluid concentra-

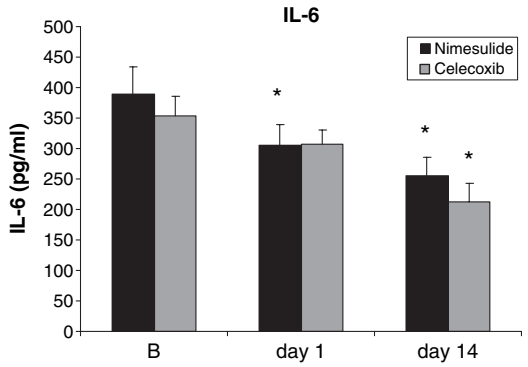

Figure 4 Synovial fluid concentrations of interleukin-6 (IL-6) measured in patients with knee osteoarthritis associated with joint effusion 30 min after drug administration on the first day (day 1) and on the last day (day 14) of treatment with nimesulide or celecoxib. *$p < 0.05$ vs. baseline (B)

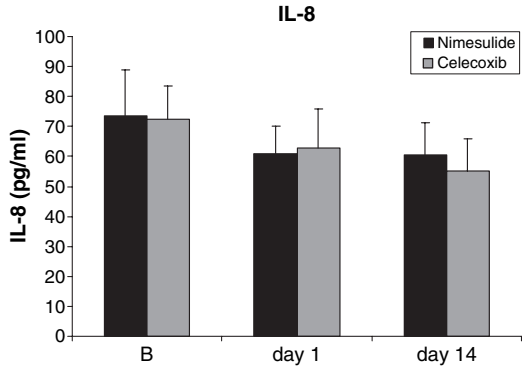

Figure 5 Synovial fluid concentrations of interleukin-8 (IL-8) measured in patients with knee osteoarthritis associated with joint effusion 30 min after drug administration on the first day (day 1) and on the last day (day 14) of treatment with nimesulide or celecoxib

tions of IL-6 did not correlate with the reduction in the intensity of pain.

Change in synovial fluid concentrations IL-8

The data regarding the measurement of synovial fluid IL-8 are shown in Figure 5. The administration of neither nimesulide nor celecoxib affected significantly the levels of this cytokine in the synovial fluid.

Patient global assessment of analgesic efficacy and tolerability

The percentage of patients who reported good or very good analgesic efficacy was 77.5% in the nimesulide group, and 50.0% in the celecoxib group (Table 3). The application of the *z*-test did not reveal any statistically significant difference.

Both drugs were well tolerated, according to patient judgement (Table 4). One patient in the celecoxib group reported episodic epigastric pain starting from the fourth day of the treatment. This trouble disappeared in 3 days without any pharmacological intervention, and the related information was given by the patient at the end of the study.

Discussion

The goal of management of knee OA is the control of pain and inflammation to facilitate an improvement in function (40). In the last few years, NSAIDs have been recognised as the preferred choice in the treatment of a number of musculoskeletal disorders, including knee OA (41,42). A body of data exist showing that the analgesic response with NSAIDs varies, and that compounds with similar pharmacodynamic characteristics may show different analgesic properties in clinical practice (34,43). We describe here the first examination of the effects of two NSAIDs, nimesulide and celecoxib, on the intensity of pain, and on the synovial fluid concentrations of SP, IL-6 and IL-8 in OA patients. No patient withdrew from the study because of adverse events, and both drugs were well tolerated. Our results confirm that both NSAIDs can significantly reduce joint pain in patients with knee OA. However, in the group of patients with joint effusion, nimesulide provided faster analgesic efficacy than celecoxib. This finding is consistent with the evidence that the concentrations of synovial fluid of SP were significantly reduced only by nimesulide. SP is released by afferent fibres that innervate the joint, it exerts pro-inflammatory and pro-algesic effects, and sensitises articular afferent fibres. In addition, it can activate immune cells and synoviocytes, induce the chemotaxis of monocytes/macrophages, and stimulate

Table 3 Analgesic efficacy according to patient judgement after 2 weeks of treatment with nimesulide or celecoxib

	Number of patients (%)				
Drug treatment	**None**	**Mild**	**Moderate**	**Good**	**Very good**
Nimesulide	–	1 (4.5)	4 (18)	12 (54.5)	5 (23)
Celecoxib	–	3 (14)	8 (36)	11 (50)	–

Total = 22 patients/group of treatment.

Table 4 Tolerability according to patient judgement after 2 weeks of treatment with nimesulide or celecoxib

	Number of patients (%)				
Drug treatment	**Very poor**	**Poor**	**Fair**	**Good**	**Excellent**
Nimesulide	–	–	9 (41)	4 (18)	9 (41)
Celecoxib	–	2 (9)	4 (18)	14 (64)	2 (9)

Total = 22 patients/group of treatment.

the production of prostaglandins and several cytokines, including IL-6 (24–26). The marked reduction in the concentrations of SP induced by nimesulide results therefore consistent with and, at the same time, may help explain the analgesic and anti-inflammatory effects of this drug in patients with OA.

Interleukin-6 is a pleiotropic cytokine that is produced by macrophages as well as by activated synoviocytes and fibroblasts. Besides contributing to joint inflammation, it plays an important role in the events responsible for the pathogenesis of OA (32,33). It has been demonstrated that IL-6 levels in the synovial fluid appear to relate directly to the stage of OA, and that the synthesis and concentrations of this cytokine are modified by pharmacological treatments aimed at reducing OA pain (27,28,44). Moreover, IL-6 contributes to pain in inflamed tissue and could facilitate the excitatory action of SP on dorsal root ganglion neurones (45). Our data show that following repeated administration, both nimesulide and celecoxib reduced the synovial fluid concentrations of this cytokine but only in patients treated with nimesulide was a significant decrease in IL-6 synovial fluid concentrations evident at 30 min after drug intake on day 1. This finding is consistent with the rapid onset of action of nimesulide against inflammatory pain. By considering the small number of patients with joint effusion, however, we cannot exclude the possibility that in a larger number of patients, celecoxib may significantly reduce IL-6 in synovial fluid also on day 1.

Previous studies showed that prostaglandins, with special reference to prostaglandin E_2 (PGE_2), stimulate the production of IL-6 by bone cells (46,47), and facilitate the release of SP from primary sensory afferents (48). The reduction in IL-6 and SP concentrations induced by nimesulide may, therefore, be explained, at least in part, with the inhibition of prostaglandin production exerted by this NSAID. With regard to this, it is interesting to note that evidence is available as to the ability of nimesulide to inhibit PGE_2 formation at the level of the joint in patients with arthritis (49). The two NSAIDs tested in this study did not affect IL-8 concentrations in the synovial fluid. These findings are in agreement with previous data obtained *in vitro*, suggesting that, unlike IL-6, IL-8 is not involved in the sensitisation of peripheral nociceptors, and that the production of IL-6 and IL-8 by human articular cells is regulated by different pathways (28,50).

Conclusion

Overall, this study suggests important clinical benefits for nimesulide 100 mg twice a day for the symptomatic treatment of OA. In patients with joint effusion nimesulide provided a rapid pain relief, with a marked reduction in the synovial fluid concentrations of inflammatory pain mediators. This is also consistent with the favourable pharmacokinetic characteristics of this drug, with special reference to its short plasma half-life. It is well known that analgesic drugs with a rapid onset of action may improve the satisfaction for patients, contribute to the ability of the patients with OA to carry out their everyday activities, and increase adherence to therapy. Thus, the results of the present trial provide further evidence that nimesulide is an effective agent for the treatment of patients with joint pain because of OA.

Acknowledgement

We are grateful to the following investigators that participated in the study: E. Baratelli, Varese, Italy; P. Ferrario, Milan, Italy. The authors would also like to thank all the patients for their participation in the study.

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Paper received December 2006, accepted April 2007

