Nimesulide, a balanced drug for the treatment of osteoarthritis

E.C. Huskisson

Edward C. Huskisson, MD, FRCP, Consultant Rheumatologist, King Edward VII Hospital for Officers, London, UK.

Address for correspondence: 14A Milford House, Queen Anne Street, London W1M 9FD, UK

Clin Exp Rheumatol 2001; 19 (Suppl. 22): S21-S25.

Key words: Osteoarthritis, nimesulide, AEs, GI-related AEs.

ABSTRACT

World-wide experience with nimesulide confirms that it is an effective anti-inflammatory drug in the treatment of osteoarthritis. A review of several studies in this condition confirms that nimesulide is at least as efficacious as other commonly used compounds. The safety profile of nimesulide, compared to reference drugs such as naproxen, etodolac and diclofenac, demonstrates superior gastrointestinal tolerability. Nimesulide is therefore a good choice for the long-term treatment of OA.

Introduction

Osteoarthritis (OA) is both common and important. It affects 15% of the world's population; it is costly and a major cause of disability in the elderly. OA has been a neglected disease, because at one time it was thought to be an inevitable part of the ageing process. Apart from misleading patients with this view, we told them that OA was non-inflammatory, and denied them the benefits of nonsteroidal anti-inflammatory drugs (NSAIDs). There is good evidence that NSAIDs are more effective than simple analgesics such as paracetamol, and they have actions other than pain relief including the relief of morning stiffness. In comparison with drugs that are only analgesic, patients overwhelmingly prefer NSAIDs. The prolonged use of NSAIDs in this chronic disease means that their long-term safety is particularly important.

As in rheumatoid arthritis and other inflammatory arthropathies, NSAIDs are the mainstay of symptomatic treatment in OA. They are effective, and many patients with OA simply cannot manage without them. The main problem is tolerability, in particular by the stomach. However, efficacy and gastric intolerability are not inextricably linked. Drugs that block mainly COX-2, thus inhibiting the formation of prostaglandins at sites of inflammation but with little effect on gastric prostaglandins that are formed mainly by COX-1, give symptomatic benefit without eroding the gastric mucosa.

Nimesulide at therapeutic doses preferentially inhibits COX-2 in man, and this is linked to the lower incidence of gastrointestinal side effects compared with common reference non-coxib compounds. Various studies, many of recent origin, confirm the general sparing by nimesulide of gastric prostaglandin formation (1). In addition, nimesulide has other properties that may contribute to the relatively low incidence of gastrointestinal side effects. These include the weakly acidic nature of nimesulide, which presumably results in relatively little gastric and renal accumulation, so partially explaining the tolerability of nimesulide by these organs. Most NSAIDs are considerably more acidic than nimesulide, and high concentrations can accumulate within the cells of the gastric mucosa/submucosa where the extracellular pH is low but intracellular pH is higher. The acidic drugs ionise inside the cells and therefore tend to be retained. The very weakly acidic nature of nimesulide (pKa 6.5) probably diminishes this retention (2).

This chapter reviews several studies in OA with the purpose of highlighting the efficacy and relative safety of nimesulide, particularly in the long-term treatment of arthritis. The percentages quoted in the text have been rounded to 2 significant figures.

World-wide experience with nimesulide

There is now a very large world-wide experience of using nimesulide to treat OA. Many studies with nimesulide in different pathologies have shown good efficacy, at least comparable to other NSAIDs,and relatively good tolerability particularly in the gastrointestinal tract. The present review of efficacy and tolerability deals with 11 studies of nimesulide in OA. In total, there were

24,785 patients, usually taking nimesulide 100 mg twice daily (bid), in open, controlled, or post-marketing surveillance studies.

Therapeutic results depend on the type of patients, their pathology, and the duration of treatment. This is particularly so in OA, where patients tend to be older, to be receiving concomitant therapies, and to show particular gastric sensitivity to NSAIDs.

Dose-finding studies

Two studies (3, 4) were performed to determine the optimal dosage of nimesulide in OA patients. The first, by Dreiser (3), compared two doses in patients suffering from OA of the hip. Two groups of 12 patients each were given nimesulide 100 mg or 200 mg bid for the first week, followed by placebo for a 7-day wash-out period, and then the other dose of nimesulide. Paracetamol was allowed as rescue medication for pain relief.

Classical variables (spontaneous pain, Lequesne Functional Index, limitation of abduction, and paracetamol consumption) were used on days 0, 7, 14 and 21 to assess the efficacy of treatment, while tolerability was determined from side-effects collected by direct and indirect questioning. A global assessment of efficacy and tolerability by patients and physicians was requested every week.

There was a significant reduction of pain scores, and improved articular function, in the nimesulide-treated groups with respect to placebo, but limitation of abduction did not change significantly during treatment in any group. Paracetamol was taken by 10 patients in the nimesulide 100 mg group, by 9 in the 200 mg group and by 15 patients during the wash-out period. In the third week of treatment there was a trend for less consumption of rescue medication. Global efficacy was assessed as good in 21%, 35% and 50% of the groups given placebo, nimesulide 100 mg or nimesulide 200 mg, respectively. Nimesulide 100 mg bid was the minimum effective dose for reducing pain and inflammation in OA of the hip.

Two patients (16.7%) in the 100 mg nimesulide group and 3 patients (25%) in the 200 mg group complained of gastrointestinal disturbances, all of which were mild or moderate. One placebo-treated patient (8.3%) withdrew because of severe gastralgia during the wash-out period. Tolerability was rated as excellent or good in about 90% of patients in each treatment group.

The second dose-finding study was a French multi-centre trial (4) of 392 patients with OA of the knee. Patients were randomly divided into four groups that were treated twice daily with placebo (n = 100) or with nimesulide 50 mg (n = 97), 100 mg (n = 98) or 200 mg (n = 97). This study, which lasted one month, assessed the optimal treatment dose for OA in terms of the efficacy/safety ratio. Again, evaluated variables (on days 0, 7, 14 and 28) were pain intensity (visual analogue scale, VAS), the Lequesne Functional Index, and consumption of the rescue medication paracetamol (up to 3 g/day, and excluding the first 3 hours of day one). Efficacy and tolerability assessments were rated on a 4-point scale by patients and physicians.

The VAS scores decreased significantly in all groups over time. Nimesulide was better than placebo at day 7 in the 100 and 200 mg groups, but the effect of 50 mg bid was not statistically significant. From day 14 on, all nimesulide groups showed a significant reduction of pain compared to placebo. Paracetamol was requested by 66% of patients receiving placebo, 57% of those given nimesulide 50 or 200 mg bid, and by 51% in the 100 mg group. The overall physicians' assessment of efficacy was excellent/good in 72% of patients given nimesulide 100 or 200 mg bid, 59% in the 50 mg group, and 42% with placebo.

As expected, there was a trend for more adverse events with the increasing dose of nimesulide, but interestingly the incidence in the placebo and 100 mg bid groups was similar (39% and 36%, respectively). Gastrointestinal side effects were dose-dependent, again with the placebo and nimesulide 100 mg bid groups showing a similar incidence. Analgesia was noted 1.5 h after taking nimesulide 100 or 200 mg, but not with 50 mg or placebo. Nimesulide is known to have a fast onset of analgesia (5, 6).

The results of this dose-finding study confirm previous data that the optimal dose with the best risk/benefit ratio for the treatment of OA is nimesulide 100 mg bid.

Comparison with placebo

Di Perri's trial (7), a double-blind study versus placebo in 40 elderly patients with OA, evaluated the efficacy of nimesulide 100 mg bid. The patients were aged 60 to 88 years, with a mean OA duration of 76 months. Two groups of 20 patients each were randomly allocated to placebo or nimesulide 100 mg bid for 3 months. Efficacy variables, measured on days 0, 30, 60 and 90, were pain at rest and on movement, morning stiffness, and impairment of daily activities. Laboratory examinations were performed on the same days to measure routine haematological and biochemical values. Nimesulide treatment significantly improved all parameters (Table I), as measured at day 90.

Tolerability was evaluated by collection of adverse events. There were reports by 4 patients (20%) in the nimesulide group (2 heartburn, 1 nausea, 1 dizziness) and 2 patients (10%) in the placebo group (1 heartburn, 1 dizziness). All adverse events were mild. Laboratory tests did not reveal any ab-

Table I. Reduction (%) of measured symptoms at day 90.

	Pain at rest	Pain on movement	Morning stiffness	Functional score
Nimesulide 100 mg bid	70.1**	67.0**	62.9*	36.9*
Placebo	11.1	16.9	28.1	13.0

*p < 0.05, ** p < 0.01, with respect to the corresponding placebo value.

normalities. This placebo-controlled study confirms the efficacy of nimesulide in the treatment of OA, in this case with elderly patients who often suffer from concomitant pathologies and receive several drugs. It is important that there is little interaction between nimesulide and other drugs (2).

Comparison with reference compounds

Nimesulide is effective and generally safe in the management of OA when compared both to other NSAIDs and to placebo. Several studies have been performed with nimesulide against reference drugs, and below are comparisons with flurbiprofen, etodolac, indomethacin, diclofenac (the best-selling NSAID in the world), and naproxen.

A multi-centre Italian study (8) compared the efficacy and tolerability of nimesulide versus flurbiprofen in 199 patients with rheumatic diseases treated for 9-13 days. The medications in this case were suppositories (nimesulide 200 mg bid, n = 99; flurbiprofen 100 mg bid, n = 100). Typical variables of pain (spontaneous and provoked) were measured by a VAS, body temperature was recorded, and haematological and biochemical tests were performed.

All variables improved significantly with either treatment, and there was an overall good/excellent assessment by both patients and physicians in more than 80% of cases. Measurement of anti-inflammatory activity against leucocytosis, increased ESR and C-reactive protein, indicated a significant superiority of nimesulide over flurbiprofen. Nimesulide induced a significantly faster antipyretic action, consistent with its known fast onset of analgesia (5, 6). There were no withdrawals from the study, and relatively few adverse events occurred (7% with nimesulide and 9% with flurbiprofen).

In a 3-month German multi-centre study (9), nimesulide 100 mg bid was compared with etodolac 300 mg bid in 199 patients with OA of the knee (n = 100, nimesulide; n = 99, etodolac). Spontaneous pain and the Lequesne Functional Index, measured at baseline and weeks 2, 4,8 and 12, improved significantly in both groups. There were no significant differences in changes of efficacy variables between the two experimental groups, but both patients and physicians gave a good/excellent assessment for nimesulide in 80% of cases compared to 68% for etodolac. Adverse events were reported by 39 patients given nimesulide, and by 34 in the etodolac group, of which 59% (nimesulide) and 64% (etodolac) were gastrointestinal. There was a significant increase of SGPT, SGOT (n = 4) and -GT (n = 2) with nimesulide, and of -GT and bilirubin with etodolac (n = 4). These did not require withdrawal from the investigation.

Comparative studies with diclofenac have been performed by many groups. A Chinese controlled trial (10) compared the efficacy and the tolerability of nimesulide and diclofenac in OA of the knee. Nimesulide 100 mg bid was given to 60 patients, and diclofenac 50 mg three times daily (tid) was given to 63 patients for 3 weeks. Efficacy was evaluated on days 7 and 21 regarding pain (at rest, on active movement and on palpation), joint swelling and walking. Tolerability was determined from recorded adverse events, laboratory tests, and overall assessment by patients and investigators.

Both treatments showed efficacy, but nimesulide was better than diclofenac ($p < 0.01$ at day 7; $p < 0.05$ at day 21). Nimesulide was clearly more effective than diclofenac according to assessments by the investigators (good/excellent, 95% for nimesulide versus 46% for diclofenac) and by the patients (good/excellent, 85% versus 42%).

The safety profile was again in favour of nimesulide, with significantly fewer patients complaining of side effects in general (13% versus 29% for nimesulide and diclofenac, respectively). Furthermore, there were even fewer gastrointestinal adverse events with nimesulide than diclofenac (6.7% versus 30% of total adverse events, $p < 0.01$). There were few laboratory changes outside the normal range in either group,and none were of clinical importance.

Another comparative study (11) with diclofenac involved 89 patients with OA of the hip or knee in a double-blind parallel-group trial. Patients were randomised to receive nimesulide 100 mg bid (n = 44) or diclofenac 50 mg tid (n = 45) for one month. Efficacy against spontaneous pain, pain on passive movement, and functional impairment, was equal in the two groups.

Tolerability was investigated by laboratory tests (haematological, biochemical and urine analysis) at the start and finish of treatment, by the physicians' overall assessment, and by endoscopy at days 7 and 30. Laboratory tests showed an increase in serum transaminases in one patient per group, and an increase of alkaline phosphatase in 3 patients given diclofenac. Assessment of tolerability by the physicians was excellent/good in 84% and 79% of the nimesulide and diclofenac groups respectively. The incidence of gastrointestinal side effects was particularly high with diclofenac (68% versus 43% with nimesulide). Endoscopies were normal in all patients at the start of treatment, but ulcers developed in one patient given nimesulide (2.4%) and in three given diclofenac (7.3%).

Long-term therapy is needed in OA, and more recently studies have examined the efficacy and tolerability of drugs over an extended period. An 'active control equivalence study' by the author (12) was performed with nimesulide and diclofenac in 279 patients with OA of the hip or knee. For 24 weeks 135 patients received nimesulide 100 mg bid, and 144 patients received 50 mg diclofenac tid. Primary efficacy measures were the patients' global evaluation of efficacy on the scale of excellent, good, fair, poor or useless, and by the Lequesne Functional Index. Secondary criteria included global pain measurement, morning stiffness, stiffness after sitting, pain at night, and the Doyle Articular Index. Adverse events were recorded, and haematological and biochemical blood tests were carried out at the beginning, in the middle, and at the end of the study.

A complex statistical method (13) found that the drugs were equally efficacious, but gastrointestinal tolerability

was better for nimesulide. Completion by patients of long studies is often poor, but surprisingly 65% and 69% in the nimesulide and diclofenac groups completed the 24 weeks. This is consistent with good long-term efficacy and tolerability. The overall incidence of adverse events was similar in the two groups: 65% of patients given nimesulide, and 68% given diclofenac, reported one or more adverse events. However, more patients in the diclofenac group had adverse gastrointestinal events (47% versus 36% with nimesulide, $p < 0.05$), and they were more likely to be worse (moderate or severe) with diclofenac. The investigators' global evaluation of tolerability using the same scale as for efficacy showed more patients with excellent tolerance to nimesulide (37% versus 24%). No serious haematological or biochemical abnormalities occurred in either treatment group. Of particular interest, there was a substantial fall in serum uric acid in the nimesulide group ($p < 0.01$), but not in those given diclofenac. Nimesulide might therefore be useful for treating gout. Azapropazone has this same effect on serum uric acid and is currently considered by many to be the most useful anti-inflammatory drug in gout.

A one-year active control equivalence study (14) compared nimesulide and naproxen in 370 patients with OA of the hip or knee who received either nimesulide 100 mg bid (n = 183), or naproxen 250 mg in the morning and 500 mg at night (n = 187). The primary endpoint was pain on the WOMAC OA index after six months. Other measures included the Lequesne Functional Index, global assessment, paracetamol consumption, and adverse events. The two drugs were similar in efficacy, and tolerability was relatively good particularly considering the patients' age (mean 64 ± 8.5 years), but again gastrointestinal side effects were somewhat less with nimesulide.

Open studies have examined the effect of nimesulide in 'real life' rather than in the somewhat structured conditions of controlled trials. A French open study (15) assessed the efficacy and tolerability of nimesulide over 3 months. The 132 OA patients took 100 mg nimesulide granules twice daily, and were assessed for pain and side effects. Haematological and biochemical analyses were made at the start and finish of the study, and the investigators assessed tolerability at the end of the study. VAS values indicated a pain reduction of 54% during the observation period, and the physicians judged the treatment as excellent/good in 77% of cases. The gastrointestinal, skin and nervous system adverse events that occurred in 33% of patients were mostly (80%) mild or moderate. Results of laboratory analyses were normal.

Post-marketing surveillance gives a 'practical' evaluation of efficacy and tolerability in a more heterogeneous population. In chronic OA, 22,938 patients (16) took nimesulide tablets or granules 100 or 200 mg bid for up to three weeks. Efficacy was rated as good or excellent in 76%, and the side effects that occurred in 9.4% were generally mild and rarely required a decrease in dosage or withdrawal from treatment (3.5% drop-out).

Nimesulide was also used by 135 asthmatic patients (0.6%) in the latter study, and only one complained of dyspnea. This is consistent with the well-established general safety of nimesulide in patients with respiratory diseases, including many of those who develop asthma with other NSAIDs (17, 18).

A meta-analysis performed by Wober (19), which included some of the studies discussed above, confirmed that nimesulide 100 mg bid for 2 weeks is at least as efficacious as other NSAIDs (piroxicam, ketoprofen, naproxen, etodolac and diclofenac) in treating OA. Furthermore, nimesulide was shown to have a superior benefit-risk ratio since it is generally about equal to placebo in safety and tolerability, especially regarding gastrointestinal adverse events.

Conclusions

Nimesulide 100 mg bid is at least as effective as other NSAIDs such as diclofenac and naproxen in OA, but is better tolerated by the stomach and side effects are generally less frequent and milder. The relatively good gastrointestinal safety of nimesulide is consistent with studies on human gastric mucosa that show at most a weak inhibition of prostaglandin synthesis (1). Nimesulide has been given to about 200 million patients, so that its safety and tolerability are well known. In addition to preferential inhibition of COX-2,nimesulide has a range of other pharmacological effects, including inhibition of various mediators of inflammation and cartilage degradation (2). It seems likely, but not yet proven, that at least some of these non-prostaglandin actions contribute to the clinical effectiveness of nimesulide.

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