

Drug Evaluation

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Nimesulide

A Preliminary Review of its Pharmacological Properties and Therapeutic Efficacy in Inflammation and Pain States

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Summary

Synopsis

Nimesulide is a new non-steroidal anti-inflammatory analgesic agent given orally or rectally on a twice daily basis in a number of inflammatory and pain states. Although still at an early stage of clinical assessment, preliminary evidence suggests that nimesulide 200 to 400mg daily is significantly more effective than placebo in reducing the pain, fever and inflammatory symptoms of chronic rheumatoid arthritis or osteoarthritis, respiratory tract infections, otorhinolaryngological diseases, soft tissue and oral cavity inflammation, dysmenorrhoea, phlebitis/thrombosis, urogenital disease and postoperative pain states. In a number of comparative studies, nimesulide has also been shown to be more effective than piroxicam (in osteoarthritis), paracetamol (acetaminophen) [in respiratory tract inflammation], benzydamine or naproxen (in otorhinolaryngological disease), phenylprenazone (in laryngotracheitis/bronchitis, respiratory inflammation and otorhinolaryngological disease), Serratia peptidases (in postoperative or dental pain, trauma and phlebitis), ketoprofen (in postoperative dental pain) and mefenamic acid (in dysmenorrhoea). In addition, the efficacy of nimesulide has been observed to be comparable with that of aspirin, with or without vitamin C, and mefenamic acid (in respiratory tract infection), ibuprofen (in soft tissue disease), naproxen (in respiratory tract inflammation, dysmenorrhoea and postoperative pain states), suprofen and paracetamol (in postoperative pain states), benzydamine (in genitourinary tract inflammation) and dipyrrone, paracetamol or diclofenac (in fever).

The safety profile of nimesulide has yet to be fully established, although initial evidence suggests the usual adverse effects associated with non-steroidal anti-inflammatory drugs occur, possibly with a lower incidence of gastrointestinal problems than with other members in its therapeutic class.

Nimesulide, therefore, appears to offer a useful alternative to other non-steroidal anti-inflammatory drugs in the treatment of patients with inflammatory conditions and/or pain and fever states. However, further definition of its efficacy and tolerability is clearly required, particularly in comparison with established or other new drugs in its therapeutic class.

Pharmacodynamic Properties

In a number of *in vitro* and *in vivo* models, nimesulide is a potent inhibitor of inflammatory activity. It has shown superior potency to indomethacin, phenylbutazone, diflumidone and aspirin in inhibiting carrageenin rat paw oedema and ultraviolet-induced erythema of guinea-pig skin. Nimesulide also produced significant antipyretic activity in a yeast-fever model in rats, and analgesic activity in the inflamed rat paws model. Nimesulide exhibited intermediate potency in inhibiting prostaglandin synthetase in bovine seminal vesicle homogenates and in carrageenin rat paw oedema models, but did not affect levels of cytoprotective prostaglandin in the gastric mucosa. There is some evidence to suggest an immunomodulatory action of nimesulide, in acting as a superoxide anion 'scavenger' from neutrophils. Preliminary studies suggest a lower ulcerogenic potential in rats, compared with a large number of anti-inflammatory drugs including indomethacin, diclofenac sodium and piroxicam.

Pharmacokinetic Properties

There are only very limited data available regarding the pharmacokinetic profile of nimesulide. In the rat, nimesulide was rapidly and completely absorbed from the gastrointestinal tract, with 95% of a radiolabelled dose recovered in urine and faeces. Single dose studies in healthy volunteers have shown plasma concentrations of 34 mg/L after a 100mg tablet. These levels were achieved 3.25 hours after administration, and the elimination half-life was 3.3 hours in these subjects. Rectal absorption and elimination was 2 to 3 times more prolonged. Repeated administration of nimesulide suppositories did not significantly affect absorption, although after 6 days the apparent elimination

half-life was extended to 24 hours. There is very little data available concerning the metabolism and distribution of nimesulide, which is of some concern.

Therapeutic Trials

Nimesulide has been used in a number of studies in patients with a variety of inflammatory diseases and pain states. Unfortunately, documentation within each therapeutic area has usually been limited, with few controlled comparative studies in large numbers of patients undertaken. In addition, the comparator drugs used have not necessarily been 'standard' anti-inflammatory agents. Some of the studies have been in patients with self-limiting diseases without placebo controls.

Nimesulide 200 to 400 mg/day has shown efficacy in alleviating the symptoms of rheumatoid arthritis and osteoarthritis with consistent improvement in spontaneous palpation or movement pain, morning stiffness, grip strength and articular flexion in non-comparative studies. In controlled studies nimesulide produced significantly greater clinical improvements than placebo, and appeared to have a better overall therapeutic profile than piroxicam in osteoarthritis in one study.

In several studies in acute respiratory tract infection, nimesulide 200mg daily was more effective than placebo in adequately controlling signs and symptoms (about 90% vs 16 to 32%). In patients with 'influenza syndrome' nimesulide 200 to 400mg daily produced similar efficacy to aspirin 2000mg daily or aspirin 1000mg plus vitamin C 600mg daily. In 2 studies of children with fever due to respiratory tract infection nimesulide 50 to 100mg suppositories 1 to 4 times daily produced better results than paracetamol 100 to 200mg 1 to 4 times daily, and nimesulide 5 mg/kg (as 1% oral suspension) produced similar efficacy to a mefenamic acid solution in terms of reducing fever, pain and inflammatory symptoms. Nimesulide 200mg daily was significantly more effective than phenylprenazone 400mg daily in one study and equally effective in another study in patients with laryngotracheitis and/or bronchitis, and has also increased the rate of symptom resolution in patients receiving antibiotic therapy. In otorhinolaryngological infections, nimesulide was considered 'useful' in most patients in non-comparative studies, and in 4 double-blind studies a 200mg daily dose was more effective and better tolerated than benzydamine 150mg daily or naproxen 500mg daily, and was either more effective or equally as effective as phenylprenazone 400mg daily. In soft tissue inflammatory diseases, nimesulide 100 to 200mg daily produced a similar improvement in pain scores and oedema reduction to ibuprofen 900mg daily. Treatment of inflammatory oral conditions has indicated superior efficacy than that with placebo or ketoprofen 200mg daily. Addition of nimesulide 200mg daily to antibiotic therapy in patients undergoing oral surgery alleviated symptoms more quickly than antibiotic therapy alone or in combination with *Serratia* peptidases. In other forms of postoperative pain or oedema, nimesulide 400 to 600mg daily was equally effective as suprofen 600 to 900mg daily, naproxen 1100 to 1650mg daily or paracetamol 500mg daily (all given by the rectal route).

Decreased menstrual pain in patients with dysmenorrhoea has been observed, with nimesulide 200mg daily being significantly more effective than placebo and mefenamic acid 500mg 3 times daily, and equally as effective as naproxen sodium 550mg daily or fentiazac 200mg daily. In patients with fever of various causes, single oral doses of nimesulide 100mg produced significant decreases in body temperature, equal to that of dipyrone 500mg and greater than that of aspirin 500mg; nimesulide 200mg suppositories were superior to placebo and equal to diclofenac 100mg suppositories. Repeated administration of nimesulide 100mg suppositories produced a slower, less pronounced, but longer duration of pain relief than paracetamol. Nimesulide has also shown potential for use in reducing pain, swelling and hyperaemia associated with phlebitis or thrombosis, where it appears to be more effective than *Serratia* peptidases. In treating symptoms of urogenital tract inflammation nimesulide (either alone or in combination with antibiotics) is superior to placebo and as effective as benzydamine 150 mg/day.

Side Effects

There are no short or long term studies in sufficiently large numbers of patients to accurately assess the side effect profile of nimesulide. However, the limited data available suggest that nimesulide produces adverse effects typical of non-steroidal anti-inflammatory drugs, the majority being associated with the gastrointestinal system, although possibly with a lower frequency than occurs with other drugs of its class with which it has been compared.

Dosage and Administration

Nimesulide is usually administered at a dosage of 100 to 200mg twice daily for the treatment of a variety of pain or inflammatory states.

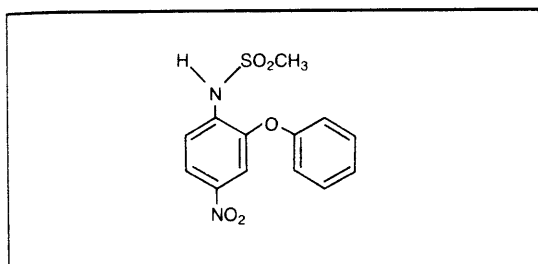


Fig. 1. Structural formula of nimesulide.

1. Pharmacodynamic Properties

The chemical formula of nimesulide is 4-nitro-2-phenoxyethanesulfonanilide (fig. 1).

1.1 Anti-Inflammatory Activity

In vitro and *in vivo* experiments on a series of ring substituted phenoxytrifluoromethane sulfonanilides showed nimesulide to be highly active in anti-inflammatory assays, but showed only moderately potent activity against bovine seminal vesicle prostaglandin synthetase (section 1.3). There was some evidence of involvement of a sulfonanilide free radical in inhibiting prostaglandin synthetase as its mode of action (Moore & Swingle 1976).

Swingle and Moore (1984) found relative anti-inflammatory potencies of 120, 41, 7, 4 and 1 for nimesulide, indomethacin, phenylbutazone, diflunidone and aspirin, respectively, in the carrageenin rat paw oedema assay. In similar experiments (data on file, Helsinn), the oral ED₅₀s for

nimesulide and indomethacin were 1.73 and 1.48 mg/kg, respectively. Effects were maximal at 3 hours and were maintained for 7 hours. Swingle et al. (1976) also found an ED₅₀ of 1.7 and 30 mg/kg for nimesulide and phenylbutazone, respectively. Again using the rat paw carrageenin oedema assay, the anti-inflammatory activity of nimesulide was found to be correlated to plasma concentrations of drug. A level of 2.5 mg/L was associated with 50% inhibition of oedema. In these tests, a late surge of anti-inflammatory activity (at 15 hours), after plasma nimesulide concentrations were approaching zero, was probably attributable to active metabolites (data on file, Helsinn).

In a model using ultraviolet-induced erythema of guinea-pig skin the ED₅₀s for nimesulide and phenylbutazone were 1.4 and 7.2 mg/kg, respectively. Oral nimesulide doses as low as 0.2 mg/kg were effective in reducing established adjuvant arthritis in rats, but not in reducing cotton pellet granulomas (Swingle et al. 1976). Swingle and Moore (1984) found nimesulide to be superior in inhibiting ultraviolet-induced erythema of guinea-pig skin compared with indomethacin, diflunidone and aspirin (ED₅₀s of 1.3, 5.0, 9.4 and 8.6 mg/kg, respectively). Carr et al. (1986) also found that the ED₄₀ for nimesulide was 0.2 mg/kg orally in an adjuvant arthritis model, compared with 0.5, 3.0 and 150 mg/kg for indomethacin, naproxen and aspirin, respectively. Böttcher et al. (1986, 1987) found nimesulide to have similar anti-inflammatory activity to indomethacin, diclofenac sodium and piroxicam in carrageenin oedema and adjuvant arthritis tests in rats.

Table I. Therapeutic indices of nimesulide and some other non-steroidal anti-inflammatory drugs, given short term to rats by the oral route (after Swingle et al. 1976)

Drugs	ED ₅₀ ^a (mg/kg)	LD ₅₀ (mg/kg)	Therapeutic index ^b
Nimesulide	1.25	324	260
Naproxen	2.10	395	190
Ibuprofen	13.5	923	68
Diflumidone	38.0	750	20
Flufenamic acid	14.7	249	17
Phenylbutazone	29.5	406	14
Acetylsalicylic acid	135	1520	11
Indomethacin	2.95	21	7

a Using carrageenin oedema assay.

b LD₅₀/ED₅₀.

In rats the ratio of LD₅₀ (lethal dose in 50% of animals) to ED₅₀ (effective dose in 50% of animals) values of a number of established anti-inflammatory compounds revealed a superior therapeutic index for nimesulide (table I; Swingle et al. 1976).

1.2 Analgesic and Antipyretic Activity

Böttcher et al. (1986, 1987) found nimesulide to have similar antipyretic activity to indomethacin, diclofenac sodium and piroxicam in a yeast-fever model in rats, similar analgesic activity in an acetic acid writhing test in rats, but far less analgesic activity than these compounds in a benzoquinone-writhing test in mice. In rats injected with carrageenin and then subjected to pressure on the inflamed paw, nimesulide 3 to 27 mg/kg provided dose-related increases in pain threshold that were significantly greater than those produced by oxyphenbutazone 6 to 8 mg/kg at 3 hours. Antipyretic activity was also greater for nimesulide than oxyphenbutazone for up to 7 hours in a brewer's yeast model in rats. Both drugs were ineffective at 24 hours (Berger et al. 1986).

1.3 Effects on Arachidonic Acid Metabolism

In an early series of experiments, several non-steroidal anti-inflammatory drugs were assessed for their potency in inhibiting prostaglandin (PG) bio-

synthesis by bovine seminal vesicle microsomes and inhibiting arachidonic acid-induced platelet aggregation. Nimesulide was found to produce a time-dependent, irreversible inhibition of prostaglandin synthetase, equally inhibiting formation of PGE₂ and PGF_{2α}. Nimesulide had an intermediate potency, being more active than aspirin or phenylbutazone, less active than indomethacin and of similar potency to flufenamic acid (Vigdahl & Tukey 1977). A subsequent study suggested that the influence of the sulfonanilide group of compounds depends on the pKa of the drug, with the more acidic compounds inhibiting prostaglandin synthesis and less acidic compounds stimulating synthesis. Nimesulide was found to have an intermediate position, with a slight degree of prostaglandin synthesis inhibition (Rufer et al. 1982). Similarly, in a comparison of effects on levels of prostaglandins in the gastric mucosa, at pharmacologically active doses, aspirin was shown to potently inhibit the production of PGE₂, 6-keto-PGF₁ and thromboxane B₂. Nimesulide and salsalate, on the other hand, did not affect the levels of cytoprotective prostaglandins or thromboxane B₂, suggesting reduced potential for gastric ulceration (Casciarri et al. 1984).

In the carrageenin rat paw oedema model, nimesulide inhibited generation of inflammatory infiltrate levels of prostaglandin E₂ and thromboxane B₂ in the inflammatory exudate (by blocking cyclo-oxygenase) for up to 24 hours (Omini 1986). In similar experiments, nimesulide was found to dose-dependently inhibit prostaglandin E₂ and thromboxane B₂ formation, and have similar activity to that of indomethacin (data on file, Helsinn). However, systemic inhibition of cyclo-oxygenase in rats (measured in *ex vivo* blood for thromboxane B₂ activity) with nimesulide was somewhat less potent than with aspirin, indomethacin or naproxen (Carr et al. 1986). Furthermore, after high doses of nimesulide 30 mg/kg inflammatory infiltrate levels of leukotriene B₄ were unchanged, unlike with some other drugs in this class where significant reductions have been observed (data on file, Helsinn).

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kg brought about a dose-dependent increase in bronchial resistance and pressure, and an increase in circulating thromboxane A₂ (determined biologically and by radioimmunoassay of TXB₂). Both nimesulide and indomethacin prevented these changes, with nimesulide being the more potent (ED₅₀s of 192 to 197 vs 320 to 332 µg/kg, respectively; data on file, Helsinn). In isolated, perfused guinea-pig lung similar results were seen with nimesulide potently inhibiting thromboxane A₂ formation following direct administration of arachidonic acid into the pulmonary artery, although indomethacin had 10-fold more activity in this test (data on file, Helsinn).

In vitro tests conducted by Böttcher et al. (1986, 1987) recorded similar inhibitory concentrations for nimesulide, indomethacin and benoxaprofen against production of hydroeicosatetraenoic acids by either murine macrophages or human polymorphonuclear leucocytes. However, against microsomal cyclo-oxygenase (IC₅₀ 2.3 mmol/L) nimesulide was considerably less active than indomethacin (2 µmol/L) or benoxaprofen (60 µmol/L); inhibition of murine macrophage PGE₂ production occurred at lower concentrations than benoxaprofen, but at higher concentrations than with indomethacin.

1.4 Immunological Effects

In vitro nimesulide has been shown to inhibit the 'respiratory burst' of phagocytosing neutrophils (shown by inhibition of chemiluminescence and inhibition of superoxide anion generation during phagocytosis of zymosan particles) without affecting their phagocytic or chemotactic responsiveness. Both nimesulide and its 4-hydroxy metabolite display this inhibition in a dose-dependent manner, without affecting the viability of the cells. It has been suggested that these effects may alter the course of inflammation, reducing tissue damage (Capsoni et al. 1987). Nimesulide has also been observed to block both classic and alternative complement activation paths by its effect on the C3 component, and again to act as a superoxide anion 'scavenger' (Auteri 1986; Auteri et al. 1988).

Table II. Comparative gastric ulcerogenic activity of selected non-steroidal anti-inflammatory drugs in stress-sensitised rats (after Rainsford 1977)

Drug	Dose (mg/kg)	Lesion index ^a
Nimesulide	100	4.6
Benorylate	200	0
Fenclofenac	100	0
Isoxicam	100	3.1
Sulindac	20	7.6
Mefenamic acid	100	8.5
Ibuprofen	100	9.0
Phenylbutazone	100	11.6
Naproxen	100	18.6
Diflunisal	100	24.4
Flurbiprofen	100	36.0
Alclofenac	100	40.8
Ketoprofen	100	42.1
Diclofenac	20	44.2
Indomethacin	20	48.0
Suprofen	100	61.0
Tolmetin	100	77.0

^a Based on number and severity of lesions.

In vivo, nimesulide has been shown to reduce polymorphonuclear leucocyte accumulation in the inflammatory infiltrate of rat paw carrageenin tests by 36% at 24 hours (data on file, Helsinn).

1.5 Effects on the Gastrointestinal System

Using a technique of cold-stress exposure in rats, which sensitises the stomach to ulcerogenic activity of drugs, nimesulide was found to have less ulcerogenic potential than all but 3 of a large series of non-steroidal anti-inflammatory drugs (table II; Rainsford 1977). Similarly, nimesulide was found to have far less ulcerogenic potential and to cause far less occult blood loss in rats than indomethacin, diclofenac sodium or piroxicam (Böttcher et al. 1986, 1987) or than indomethacin or naproxen (Carr et al. 1986).

1.6 Miscellaneous Pharmacodynamic Effects

In vitro experiments on isolated rat myometrium have shown nimesulide to reduce or eliminate the contractile activity in this smooth muscle

preparation. Nimesulide abolished the reaction of the myometrium to oxytocin, vasopressin, and bradykinin, although exogenous prostaglandin $F_{2\alpha}$ restores the myometrial reactivity to those polypeptides (Malofiejew & Blaszkiewicz 1979).

Nimesulide has also been shown to dose-dependently reduce experimental bronchospasm and thromboxane A_2 in response to a variety of substances, including histamine, bradykinin, leucotriene C_4 and sensitisation with ovalbumin, in rats (Omini 1986) and guinea-pigs (data on file, Helsinn). In contrast, indomethacin only inhibited bradykinin-induced bronchospasm in rats (Omini 1986). These results indicate that in addition to inhibiting arachidonic acid metabolism, nimesulide, in contrast to indomethacin, may directly inhibit other systems such as the histaminergic system and the anaphylactic phenomenon.

1.7 Toxicology

Long term toxicity studies of oral nimesulide 10 to 60 mg/kg/day over periods of 12 to 21 months have revealed gastrointestinal pathology, but little or no effect on other organ systems. Nimesulide-induced ulcerative gastroenteric alterations were associated with a dose-related increase in mortality. Bodyweight and food consumption were unaltered and no toxicity was observed on eyes, kidneys, liver or haemopoiesis. Secondary neutrophilia and anaemia were occasionally reported. In dogs, administration of nimesulide 10 to 60 mg/kg for 1 year revealed no drug-related toxicity (data on file, Helsinn).

Nimesulide showed no evidence of mutagenicity in 3 tests (Ames test in *Salmonella typhimurium*; forward mutation in *Schizosaccharomyces pombe*; mitogenic gene conversion and mitotic gene conversion in *Saccharomyces cerevisiae*). Similarly, there was no evidence of a clastogenic action of lymphocyte chromosomes *in vitro*, and no incorporation of ^3H -thymidine in cultured human lymphocytes (data on file, Helsinn).

2. Pharmacokinetic Properties

Published pharmacokinetic data are limited largely to findings in animals. Nimesulide has been shown to be promptly and almost completely absorbed from the gastrointestinal tract of the rat, with peak plasma concentrations of 4.5 mg/L being reached at 3 hours following single oral doses of 1.5 mg/kg. About 70% of the dose is excreted in faeces and about 23% in urine, with an overall recovery of ^{14}C -radiolabelled compounds of about 95%. Similar urinary:faecal ^{14}C recovery ratios after intravenous administration suggests extensive biliary excretion. The mean terminal elimination half-life in rats was 3.4 hours, with no retention of radiolabelled drug in plasma or tissues after single intravenous doses. Several metabolites, but no unchanged drug, were detected (Chang et al. 1976).

A limited number of, mostly, unpublished studies have also examined the pharmacokinetic properties of nimesulide after single and repeated doses in healthy volunteers.

Following single 100mg oral doses in healthy volunteers peak plasma nimesulide concentrations were significantly higher (68 mg/L), more rapidly achieved (2.25 hours) and elimination half-life was more prolonged (4.95 hours) after administration as 5% drops, than after administration as a 1% suspension (46 mg/L; 3 hours; 3.85 hours) or tablets (34 mg/L; 3.25 hours; 3.3 hours). These formulations did not differ significantly from each other in terms of absorption, but produced higher and more rapid peak nimesulide plasma concentrations than a suppository formulation (table III; data on file, Helsinn).

An earlier comparison between a non-micronised tablet and a micronised tablet in dogs and healthy male volunteers showed that significantly greater AUC values (by 2-fold), and higher peak plasma concentrations were achieved earlier with the micronised formulation, and indeed it is this formulation that was used in subsequent clinical studies (Chang et al. 1975a,b).

In a repeated administration pharmacokinetic study, nimesulide 200mg suppositories were given twice daily for 6 days to 6 healthy volunteers. Al-

Table III. Summary of single-dose nimesulide pharmacokinetic studies

Reference	No./type of patients	Dose and formulation	C _{max} (mg/L)	t _{max} (h)	AUC (g/L · h)	t _{1/2} (h)
Bernasconi & Massera (1985)	12 healthy adults	100mg, 5% drops	68.5	2.25	515.8	4.95
		100mg, 1% suspension	46.5	3.00	355.2	3.85
		100mg, tablets	34.2	3.25	268.6	3.30
		200mg, suppositories	13.9	9.0	341.4	7.07
Data on file, Helsinn	45 children	100mg, suppositories	75	3.0	671	3.15

Abbreviations: C_{max} = peak plasma concentrations; t_{max} = time to reach peak plasma concentrations; AUC = area under the concentration-time curve; t_{1/2} = elimination half-life.

though there was some variability in mean peak plasma concentrations over the 6-day treatment period, they were attained at 7.2 hours and appeared to reach steady-state after only 1 day. However, the apparent elimination half-life of nimesulide after 6 days was 24.7 hours (about 3 times that seen after single-dose administration of suppositories) indicating that the drug may accumulate in a tissue compartment. At 3 days after administration plasma nimesulide concentrations were about 10-fold lower than mean steady-state levels (data on file, Helsinn). Experience in a number of unpublished studies in Italy has shown that nimesulide tablets and granules are better absorbed on a full stomach than in the fasting state, with peak plasma concentrations of 6 to 10 mg/L and 2 to 6 mg/L, respectively. In addition, it was found that the plasma elimination half-life of nimesulide was significantly longer (no details) than that of an unnamed active metabolite (2 to 7 hours) [Ambrosini 1986].

Nimesulide concentrations in human female reproductive tissues after single oral 100mg doses reached 0.9 µg/g at 2.3 hours (72% of serum levels) and showed a progressive increase over the first 3 hours in all patients (data on file, Helsinn).

There is little other information regarding metabolism and distribution of nimesulide in humans, with the exception of one study which showed extensive concentration-dependent plasma protein binding (99.3% at 10 mg/L). Salicylic acid and nimesulide produced significant mutual displacement from plasma proteins, while tolbut-

amide caused only slight displacement of nimesulide. Nimesulide did not affect warfarin binding (data on file, Helsinn).

3. Therapeutic Trials

3.1 Rheumatoid Arthritis and Osteoarthritis

Nimesulide has shown potential in a limited number of studies for use in the treatment of symptoms of rheumatoid arthritis and osteoarthritis. Four non-comparative studies in small numbers of patients have shown nimesulide to improve disease parameters significantly and consistently, such as spontaneous pain, pain on movement or palpation, morning stiffness, articular rigidity, grip strength and quality of sleep (table IV; fig. 2; Merchant et al. 1982; Reiner 1982; Reiner & Magni 1982; data on file, Helsinn). In another study nimesulide 200 to 600 mg/day produced improvements or resolution of symptoms in 30 of 32 patients with arthrosis, but in only 4 of 8 patients with rheumatoid arthritis (Weissenbach 1981).

In a double-blind placebo-controlled study, nimesulide 200 mg/day or placebo was administered in a crossover fashion for 7 days each to 40 patients with a variety of degenerative arthritic conditions. During the sequence nimesulide-placebo, nimesulide and placebo were associated with 45% and 21% reductions in symptoms; during the placebo-nimesulide sequence, symptoms were reduced by 12% and 58%, respectively. Total clinical evaluations for these two sequences at days 0, 7 and 14 were 8.71, 4.79 and 3.77; and 8.14, 7.15 and 3.02, respec-

tively. Extra analgesics were required by 4 patients receiving nimesulide and 13 patients receiving placebo (Gamarski 1981). In two studies, erythrocyte sedimentation rate was reduced in arthritics treated with nimesulide (Gamarski 1981; Reiner & Magni 1982) and in the latter study haemoglobin also fell. However, no other laboratory or biochemical parameters were significantly altered in these studies.

In a controlled comparative study, 39 patients with osteoarthritis received either nimesulide 200 to 400 mg/day ($n = 20$) or piroxicam 20 to 30 mg/day ($n = 19$) for a mean of 10 days (Ventura et al. 1985). Overall efficacy was judged to be excellent in 20 and 0%, average in 70 and 79% and non-existent in 10 and 21%, respectively. Both nimesulide and piroxicam produced significant im-

provements after 1 week in individual assessment parameters (pain on passive or active movement, pain on palpation and articular stiffness). Global tolerability was judged to be excellent in 19 patients and poor in 1 patient (gastralgia) receiving nimesulide. Piroxicam tolerability was excellent in 4 patients, average in 14, and poor in 1 patient. In a subsequent non-comparative study in a further 15 patients with rheumatic disease, a granular (not tablet) preparation of nimesulide was associated with excellent results in 7 and average outcome in 8 patients. Improvements in pain on active movement, passive movement, palpation and articular stiffness were observed in 60, 66, 80, and 80% of patients, respectively.

Clearly, further controlled studies against pla-

Table IV. Effect of nimesulide on rheumatic disease parameters

Study A: Nimesulide 100 to 300 mg/day for 10 to 20 days in 11 patients with chronic osteoarthritis of the cervical spine (after Reiner 1982)

Day	Spontaneous pain ^a	Pain on movement ^a		Quality of sleep ^a	Morning stiffness (min)
		passive	active		
0	2.18	2.9	2.4	1.64	65.6
1	1.27	2.0	1.4	2.36	31.9
5	1.10	1.44	1.22	2.20	15.0
10	0.56	0.57	0.43	2.89	10.7
15	0	0.20	0	2.40	0

Study B: Nimesulide 200 mg/day for 20 days in 10 patients with rheumatoid arthritis (after Merchan et al. 1982)

Day	Spontaneous pain ^b	Pain on movement ^b		Pain on palpation ^b	Articulate rigidity ^b
		passive	active		
0	1.7	2.1	1.7	1.5	2.1
10	1.3	1.5	1.3	1.3	1.7
20	0.7	0.9	0.5	0.6	0.9

Study C: Nimesulide 400 mg/day for 14 days in 10 patients with rheumatoid arthritis (after Reiner & Magni 1982)

Day	Spontaneous pain ^{a,c}	Pain on movement		Grip strength (mm Hg) ^d	Morning stiffness (min)	Articular index	Functional index
		passive	active				
0	2.05	1.0	2.56	109	113.5	18.9	13.4
14	1.15	0.44	1.67	166	39.5	12.3	10.6

a Analogue scale (0-4).

b Analogue scale (0-3).

c Composite of day and night scores.

d Composite of left and right hands.

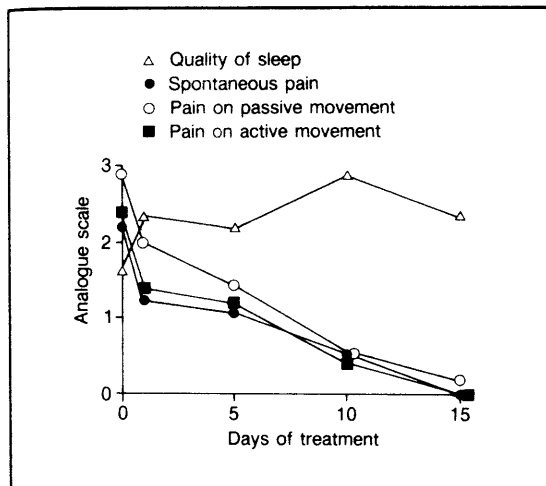


Fig. 2. Effects of nimesulide 100 to 300 mg/day on some clinical parameters of efficacy in 11 patients with osteoarthritis of the cervical spine (after Reiner 1982).

cebo and other non-steroidal anti-inflammatory agents must be undertaken.

3.2 Respiratory Tract Inflammation

Nimesulide has been compared with a number of other therapeutic regimens in controlled studies of patients with acute respiratory tract infections. In 40 adult patients with chronic bacterial inflammatory disorders of the lung or with painful neoplasms, nimesulide 100mg twice daily for 5 to 15 days was administered (either as tablets or granules), in addition to antibiotics in 31 patients. Assessments of spontaneous pain, dyspnoea and exercise, cough, and sputum volume were all significantly improved by 5 days and continued to do so throughout the study period. Symptomatic improvement occurred in over 70% of patients, and in the context of the chronic nature and severity of the patients' condition is probably attributable to nimesulide (Figueroa et al. 1986). In 2 double-blind studies of 51 and 44 patients, respectively, with acute upper respiratory tract infection (origins not given), nimesulide 100mg twice daily or placebo were given for 4 to 7 days (Emami Nouri 1984; Tomassini et al. 1986). Nimesulide was signifi-

cantly more effective than placebo in reducing all signs and symptoms of infection (table V). Global rating scales showed that nimesulide was considered useful in 22 of 24 patients (92%) compared with placebo which was considered useful in only 4 of 25 patients (16%) [Emami Nouri 1984] or achieved 'excellent or good' resolution in 20 of 22 patients (91%) compared with 7 of 22 patients (32%) given placebo (Tomassini et al. 1986). There were no adverse effects associated with nimesulide in these studies.

Nimesulide has been compared with phenylprenaline in 3 studies. Allegra (1986) reported treatment of 100 patients with laryngotracheitis and/or bronchitis with either nimesulide 100mg twice daily ($n = 53$), or phenylprenaline (no dose stated; $n = 47$) for 7 days. Nimesulide produced significantly greater reduction in cough and dyspnoea, and an equal reduction in mucous membrane congestion than phenylprenaline. Similarly, in 36 patients with chronic upper respiratory tract inflammation (probably of viral origin) treated with nimesulide 100mg twice daily or phenylprenaline 200mg twice daily for 10 days significantly reduced symptoms – pharyngeal mucosa congestion and oedema, dysphonia, dysphagia and cough – with overall efficacy being rated as 'excellent' in 53 and 12%, respectively (Resta et al. 1987). In 40 patients with acute or chronic respiratory tract inflammation not indicative of bacterial infection were randomised to receive nimesulide 100mg twice

Table V. Effects of nimesulide 100mg twice daily or placebo on signs and symptoms of acute upper respiratory tract infections (Emami Nouri 1984)

Symptom	No. of symptom-free patients in 4 days	
	nimesulide	placebo
Hoarseness	14/23	5/24
Sore throat	12/18	3/18
Headache	10/18	4/18
Arthralgia	6/12	0/9
Tonsillar redness	9/15	1/15
Tonsillar swelling	6/15	1/13
Pharyngeal redness	15/24	0/25

daily or phenylprenazone 200mg twice daily for 7 days. The drugs produced significant and similar reductions in clinical symptomatology – pharyngeal congestion, pharyngeal oedema and cough. Objective measurements, such as rhinomanometric examination (0.64 to 0.75; 0.58 to 0.66, respectively) and nasal mucociliary transit time (27.1 to 22.1; 29.0 to 26.8, respectively) also showed improvements with both drugs. There were 3 and 4 cases of epigastralgia, respectively (data on file, Helsinn). In a similar group of 45 patients with upper respiratory tract infection of bacterial origin, patients received ampicillin 2 to 3g daily in combination with either nimesulide 100mg 3 times daily, naproxen 275mg 3 times daily or placebo for a period of 6 days. Both active therapies reduced the main clinical symptoms of oropharyngeal hyperaemia, tonsillar hypertrophy and odinophagia significantly, and to a greater extent than with placebo (fig. 3). Other less prevalent symptoms, such as adenomegaly, myalgia and arthralgia, were also reduced by therapy. Overall assessment revealed good to excellent results with nimesulide in 93%, naproxen sodium in 86% and placebo in 74% (data on file, Helsinn).

Several other studies have measured the anti-inflammatory, antipyretic, and analgesic effects of nimesulide in patients with 'influenza-like syndrome'. Two such studies have used granule formulations of test drugs. Milvio et al. (1986) and Bernasconi and Massera (1985) compared nimesulide 100mg twice daily with aspirin 500mg plus vitamin C 300mg twice daily, and found both treatments to be associated with excellent results over a 7-day study period. Most symptoms (sore throat, cough, cephalgia and articular pain) were resolved within 4 days with either therapy, and complete recovery was seen in over 90% of patients treated. In both studies the adverse effect profile favoured nimesulide, with only 1 of 19 and 2 of 22 patients experiencing gastralgia, respectively, compared to 5 of 20, and 8 of 22 patients treated with aspirin, including 2 patients in the latter study whose side effects required withdrawal from the trial (Bernasconi & Massera 1985; Milvio 1986). Another study in 50 patients with 'influenza syndrome' compared the effects of nimesulide 200mg twice daily with those of aspirin (1000mg twice daily) both given as suppositories for at least 6 days. Again symp-

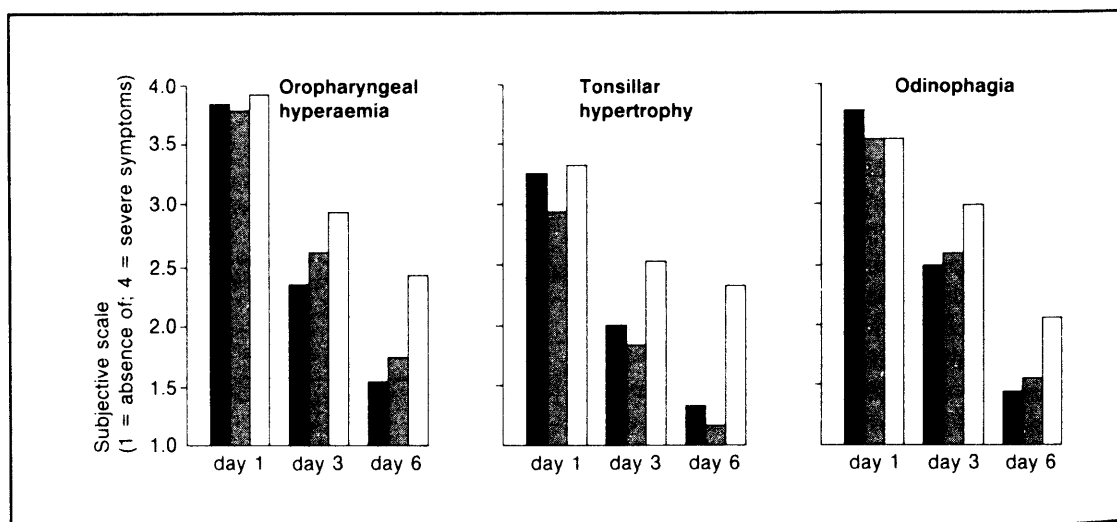


Fig. 3. Effect of treatment with ampicillin 2 to 3g daily in combination with nimesulide 100mg bid (■), naproxen 275mg tid (▨) or placebo (□) on symptoms of acute or chronic upper respiratory tract inflammation (data on file, Helsinn).

Table VI. Effects of treatment with nimesulide 200mg or aspirin 1000mg (twice daily suppositories) on signs and symptoms of influenza syndrome' (after Milvio 1985)

Symptom	Nimesulide			Aspirin		
	no. of pts	base value	end value	no. of pts	base value	end value
Pharyngeal redness	20	2.05	0.50	21	2.04	0.70
Sore throat	22	2.18	0.55	23	2.21	0.65
Hoarseness	8	2.00	0.50	7	1.71	0.14
Cough	10	2.40	0.50	16	2.31	0.87
Nasal obstruction	18	2.55	0.56	21	2.71	0.76
Rhinorrhoea	9	2.55	0.56	11	2.54	0.82
Cephalaea	25	2.52	0.60	25	2.64	0.80
Articular pain	24	2.50	0.54	24	2.45	0.58
Asthenia	23	2.17	0.91	22	2.00	0.91
Lack of appetite	16	1.75	0.87	9	1.77	0.78

toms were almost completely resolved within 7 days (table VI) with 23 of 25 and 21 of 25 patients considered to have shown a good or fairly good response, respectively (Milvio 1985).

A double-blind trial was conducted in 45 hospitalised patients requiring antibiotic therapy for acute or chronic respiratory infections, comparing the efficacy of antibiotic therapy alone (mostly ceftriaxone or amoxycillin) with antibiotic plus either nimesulide 100mg or placebo twice daily for 15 to 23 days. Patients in the antibiotic plus nimesulide group experienced significantly greater and more rapid improvement of signs and symptoms such as chest pain, cough, fever, oropharyngeal hyperaemia, asthma and osteoarticular pain (Reiner 1983).

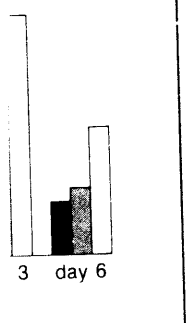
In 60 children with upper respiratory tract infection and fever, nimesulide 5 mg/kg (as a 1% oral suspension) was compared with a mefenamic acid solution over a 3- to 10-day treatment period. Both drugs produced rapid and significant decreases in body temperature and inflammatory symptoms (Salzberg 1986). In a similar study by the same investigator, nimesulide 50 or 100mg suppositories and paracetamol (acetaminophen) 100 or 200mg suppositories were given 1 to 4 times daily for a maximum of 5 days to 57 children with (mostly) upper respiratory tract infections. Nimesulide was significantly better than paracetamol in reducing fever, pain and other symptoms (Salzberg 1985).

3.3 Otorhinolaryngological Inflammation

Storme and LeBacq (1985) treated 49 adult patients with ear, nose and throat inflammations with nimesulide 50mg twice daily for 11 days. Antibiotics (n = 26) and other anti-inflammatory/analgesic drugs (n = 7) were also given to some patients. On an analogue scale, average symptom score was reduced from 5.2 to 1.0 at the end of treatment, including 25 symptom-free patients. Nimesulide was considered useful by 60% of patients and 55% of doctors, however the extent to which a lack of comparative treatment group invalidates the results is not discussed. Treatment was also associated with decreased leucocytosis, C-reactive protein and transaminases and increased thrombocytes and blood urea levels, although these changes were still within normal limits. Erythrocyte sedimentation rate and fibrinogen levels were unchanged. In another non-comparative trial in 400 patients with otorhinolaryngological disorders, treatment with nimesulide 100mg twice daily for 4 to 12 days was associated with decreases in pain and oedema from day 2, and produced excellent results in 73% of patients (Ferretti & Zollo 1987).

Nimesulide 200mg daily was compared in 3 blinded studies, with benzydamine 75mg twice daily in 50 patients (Milvio 1984), with naproxen 500mg daily in 53 patients (Emami Nouri 1986) and with phenylprenazone 200mg twice daily in 40 patients

agia



ken 275mg tid (■) or

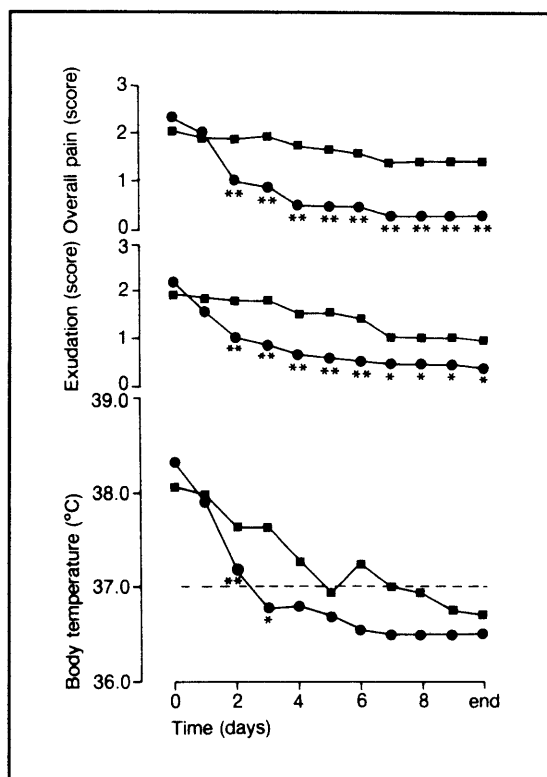


Fig. 4. Effects of nimesulide 200 mg/day (●) or benzydamine 150 mg/day (■) on overall pain, exudation and body temperature in 50 patients with otorhinolaryngological inflammatory disease (after Milvio 1984); * = $p < 0.05$, ** = $p < 0.01$.

(Mantovani & dal Prà 1987). In the former study, nimesulide brought about a rapid improvement in overall pain, exudation, fever, oedema and headache, and was significantly more effective than benzydamine (fig. 4). Pain intensity was decreased by 88% in 3 days with nimesulide, but by only 33% in 6 days with benzydamine. In addition only 1 patient experienced gastralgia and drowsiness after nimesulide compared with 11 patients on benzydamine (Milvio 1984). Administration as a granular formulation produced 'useful' efficacy in 25 of 27 (92.5%) patients receiving nimesulide, compared with 16 of 26 (61.6%) receiving naproxen. Symptoms of pain, exudation, oedema and headache were judged to be rapidly relieved, although no data are given. Both drugs were well tolerated, with only 2 cases of gastralgia with naproxen being reported

(Emami-Nouri 1986). In the third study, both groups showed significant improvements in clinical symptomatology in all patients, but with no differences between groups (Mantovani & dal Prà 1987).

One published study reported the results of 3 non-blind comparative or non-comparative studies of nimesulide in otorhinolaryngological disease (Ottaviani 1986). In one group of 25 patients with otitis, nimesulide 100mg twice daily for 7 days reduced tympanic inflammation in 50% of patients and also reduced pain, hypoacusia, autophony and tinnitus. Pain was more effectively reduced than with phenylprenazone, although no details are given. In another group of 18 patients with rhinosinusitis, nimesulide (no dosage details) reduced high endonasal pressure (from 21.4 to 18mm Hg) and increased cavity airflow (from 13 to 14.5 L/min). Nimesulide also reduced oedema and normalised the accelerated mucociliary transport rate. In the third group, 24 patients with acute laryngotonsillitis experienced effective antipyretic, analgesic and decongestant action (no details given) following nimesulide 100mg twice daily for 7 days, given either alone or in combination with cephalexin.

40 adult patients with secretory otitis media were randomised to receive either nimesulide 100mg twice daily or phenylprenazone 200mg twice daily for 10 days. The number of patients experiencing subjective symptoms of pain, tinnitus, hypoacusia and autophonia were significantly reduced: pain (4 to 1 vs 5 to 0); tinnitus (19 to 7 vs 10 to 5); hypoacusia (36 to 19 vs 35 to 22); autophonia (12 to 4 vs 16 to 8), respectively. Objective measurements were also improved. Tube function was normalised in 50% and 32.5%, respectively, tympanic normalisation occurred in 40% and 17.5%, respectively. Moreover, there was a reduction in patients with type B classification (endotympanic swelling giving reduction of tympanic mobility) from 78 to 15% and from 90 to 30%, respectively. Gastric complaints were observed in 3 patients receiving nimesulide and 7 receiving phenylprenazone (Pascali et al. 1988).

3.4 Soft Tissue and Oral Cavity Inflammation

In a non-comparative study, nimesulide 200 to 600mg daily was administered to a group of patients with a variety of subacute or chronic rheumatic diseases, including 28 patients with tendinitis. In this subgroup, treatment for a mean duration of about 25 days produced either improvement or resolution of the condition in 26 of 28 (93%) of patients (Weissenbach 1981).

In a subsequent double-blind study, Lederman and Rubinstein (1982) treated 80 patients with soft tissue inflammatory disease – muscle pain, fibrositis, tendinitis, bursitis, tenosynovitis – with nimesulide 50 to 100mg twice daily or ibuprofen 300mg 3 times daily for 7 days. Overall pain scores were significantly reduced by both drugs (from 6.05 to 3.2 and from 6.85 to 2.95, respectively) as was oedema, in 15 of 18 and 10 of 18 patients, respectively. Overall physician assessment of clinical activity was good or excellent in 29 of 39 (74%) and 27 of 38 (71%) patients, respectively.

Treatment of inflammatory oral conditions with nimesulide has been studied in 2 similarly designed double-blind trials. Cornaro (1983) treated 49 patients with postoperative inflammation after oral surgery with nimesulide 200 mg/day or placebo. Nimesulide was significantly superior to placebo for all symptomatic measures of analgesia or anti-inflammatory activity, and was more rapidly effective. Overall ratings of 'excellent or good' were achieved in 64% and 25% of patients, respectively. Withdrawal from the trial due to lack of efficacy occurred in 1 and 7 patients, respectively. In the other study, 20 patients with painful temporomandibular joint and 26 patients undergoing impacted third molar extraction were randomised to receive nimesulide 100mg twice daily or ketoprofen 200mg daily for 2 weeks (the latter group also received amoxycillin 3 g/day for 6 days). By the second week, 9 of the 10 patients in the nimesulide-treated group obtained significant relief from pain and muscle contraction, and 8 of 10 showed remission from headache. Results for the ketoprofen group were 4 of 8, 7 of 8 and 4 of 8 patients, respectively. At the end of treatment all patients were free from pain

and oedema, however nimesulide had a more rapid action with 12 of 13 patients being free of these symptoms at 7 days compared with only 9 of 13 ketoprofen-treated patients. Regarding adverse effects, gastritis occurred in 1 and 3 patients, respectively, and 1 patient in the ketoprofen group experienced a severe asthmatic reaction combined with cutaneous rash requiring treatment withdrawal (Moniaci et al. 1988).

100 patients undergoing oral surgery for simple tooth extraction, extraction of impacted or semi-retained third molars, or for osteolysis, received 6 days' treatment with amoxycillin 1500 mg/day and either nimesulide 200 mg/day (n = 40), *Serratia* peptidases 15 mg/day (n = 40) or no additional therapy (n = 20). At the end of therapy, nimesulide was associated with an 'excellent' clinical outcome (reduction in pain and swelling) in 65% and a 'good' outcome in 30%. Results were recorded as 'excellent' in 40% and 'good' in 25% of those treated with *Serratia* peptidases, and as 'excellent' and 'good' in 5% and 20%, respectively, after placebo. Nimesulide also had a more rapid clinical effect. There were no withdrawals attributed to side effects of drugs, although data on side effects not causing withdrawal of treatment were not presented. The differences between treatments were more obvious in patients undergoing removal of impacted or semi-retained third molars than in simple extraction or surgery for osteolysis (Salvato et al. 1984). In a further 100 patients undergoing dental operations (extractions, apical granulomas, retained or eruptive third molars), treatment consisted of bacampicillin given alone (n = 20), or in combination with either nimesulide 100mg twice daily (n = 40) or *Serratia* peptidases 15 mg/day (n = 40). Few details of study results were presented, although the nimesulide-bacampicillin combination was associated with significantly better clinical outcome than the other two treatments (Bucci et al. 1987).

3.5 Dysmenorrhoea

The effects of nimesulide 100mg on intrauterine pressure and pain were assessed in 2 studies of women with primary essential dysmenorrhoea. Us-

ing a microballoon-tipped catheter on the first day of menstrual flow (maximal pain), nimesulide was found to significantly decrease resting and active uterine pressures, and cyclic active pressure frequency at 1 to 2 hours (table VII). On a 0 to 4 analogue scale, pain severity was also significantly reduced (Pulkkinen 1984, 1987). Pain relief occurred at 19 minutes and was maximal at about 47 minutes after nimesulide administration (Pulkkinen 1984). Concentrations of menstrual fluid prostaglandin F_2 were also lowered, from 382 to 94 $\mu\text{g/L}$ (Pulkkinen 1987). 14 women then entered a double-blind crossover study of nimesulide 200 mg/day or placebo each administered for 2 menstrual cycles. Therapy was considered 'good' and 'very good' in 22 of 28 cycles (79%) with nimesulide, but in only 9 of 27 cycles (33%) treated with placebo (Pulkkinen 1987).

In 2 other double-blind placebo-controlled studies, women with severe primary essential dysmenorrhoea were treated with nimesulide 200 mg/day, starting 3 or 4 days before anticipated menstruation and finishing on the fifth to seventh day of the cycle. Treatment was repeated for 3 or 4 menstrual cycles, respectively (Moggian et al. 1986; Rondel et al. 1984). Nimesulide significantly decreased both severity and duration of symptoms (headache, abdominal pain, backache) in 10 of 12 patients compared with 2 of 12 patients given placebo (Rondel et al. 1984) and was associated with 'very good or good' subjective results in 72.5% vs 6.5% of patients, respectively (Moggian et al. 1986). In the latter study a lower dose of nimesulide (100mg daily) was significantly less effective. In ad-

dition to the overall responses, consumption of additional analgesics/antispasmodics was significantly decreased compared with placebo.

60 women with severe long-standing dysmenorrhoea were treated with either nimesulide 100mg twice daily, fentiazac 100mg twice daily or mefenamic acid 50mg 3 times daily for 5 days before the start of menstruation for 3 consecutive cycles. All 3 therapies produced reductions in menstrual pain, with nimesulide and fentiazac being active from day 1 and mefenamic acid from day 2 of each cycle. Both nimesulide and fentiazac were also significantly more effective than mefenamic acid. Nimesulide was more effective than fentiazac on days 2 and 4 of the cycle, whereas fentiazac was more effective on day 3. Other symptoms which commonly occurred, such as nausea, dizziness and headache, were also all significantly reduced, and absence from work or incapacity were reduced by 95% with nimesulide and fentiazac and 60% by mefenamic acid. Global evaluations by physicians concluded that 'good or satisfactory' results were obtained in 95%, 90% and 85% with the 3 treatments, respectively (data on file, Helsinn).

Nimesulide 200mg and naproxen sodium 550mg (both given by the rectal route) were compared over 1 cycle in an unstated number of women with primary and secondary dysmenorrhoea. Both treatments were stated to significantly improve painful symptoms and were well tolerated even in patients with nausea and gastric discomfort, although no data are available. Results were better in the second cycle of treatment regardless of drug (Gianella & Schmid 1985).

Table VII. Effect of nimesulide 100mg on intrauterine pressure in women with primary dysmenorrhoea

Reference	No. of pts	Resting pressure (mm Hg)		Active pressure (mm Hg)		Pressure frequency (/15 min)		Overall pain score	
		baseline	nimesulide	baseline	nimesulide	baseline	nimesulide	baseline	nimesulide
Pulkkinen (1984) ^a	6	36.7	17.2	113.3	44.2	11	7	3.17	1.83
Pulkkinen (1985) ^b	23	31.2	16.2	84.2	44.2	10.5	7	3.20	1.67

a Measurements taken 1 hour after dosing.

b Measurements taken 2 hours after dosing.

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In one study, 30 women specifically diagnosed as having menstrual headache were treated in a double-blind fashion with either nimesulide 100mg 3 times daily or placebo, beginning at the start of headaches, and continued for 9 days. Using a total pain relief scoring method there was a highly significant difference both for intensity and duration of headache in favour of nimesulide in all 3 cycles studied (Gallo et al. 1988).

3.6 Surgical Pain States

Schmökel and Brunner (1985) assessed a regimen of elevated bed-rest and anti-inflammatory drugs in the prevention and treatment of post-traumatic and/or postoperative oedema in patients with cerebral trauma or disease. Nimesulide 400 to 600 mg/day, suprofen 600 to 900 mg/day and naproxen 1100 to 1650 mg/day (all given as suppositories) were all shown to rapidly reduce postoperative pain and oedema, and the rectal route of administration allowed immediate and uncomplicated administration of drugs. Schmökel et al. (1985) also undertook a double-blind comparison of nimesulide 400 mg/day and paracetamol 500 mg/day (both given as suppositories) in patients with moderate to severe postoperative pain. After a single dose, to 53 patients, the two drugs were equally effective in reducing the analogue pain score (by 32% and 25%, respectively) after only 30 minutes. However, pain score in both drug groups had begun to increase again 6 hours after the first dose. Repeated administration to a further 17 patients showed a diminution of 73% and 79% in the mean analogue pain score for the 2 groups, respectively, after 2 days. At this point, oedema was also significantly reduced, by about 17% in both groups.

3.7 Fever

Three double-blind studies have assessed the antipyretic efficacy of nimesulide in patients with fever of various aetiology. In one trial 18 hospitalised patients with a body temperature over 38°C received single oral doses of either nimesulide 100mg, aspirin 500mg or dipyrone 500mg. Signifi-

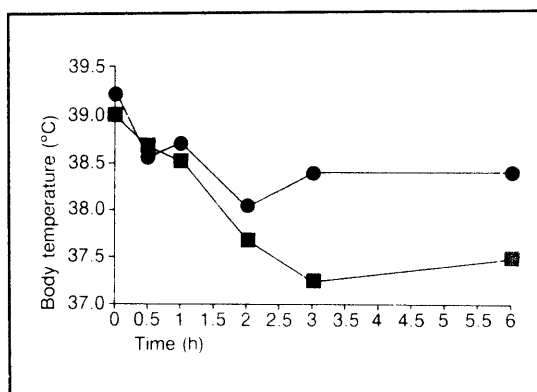


Fig. 5. Effect of treatment of fever in children (n = 22) with nimesulide 100 to 400 mg/day (■) or paracetamol 200 to 800 mg/day (●) [data on file, Helsinn].

cant decreases in body temperature were recorded at 6 hours after nimesulide and dipyrone (both reduced from 38.4 to 36.75°C), but the decrease was less with aspirin (from 38.6 to 37.6°C). Nimesulide also reduced fever-related increased pulse rate (from 95.3 to 83.4 beats/min) whereas the other drugs had no significant effects (Reiner et al. 1984).

Nimesulide 200mg suppositories, diclofenac 100mg suppositories and placebo were given to another 81 febrile patients. Six hours after administration, both drugs had significantly reduced body temperature (from 38.6 to 36.6 and 36.5°C, respectively) whereas the reduction after placebo (from 38.6 to 38.0°C) was not significant. Pulse rate was reduced by nimesulide (from 97.0 to 84.3 beats/min) and diclofenac (from 100.6 to 85.2 beats/min), but not by placebo. In addition, arterial blood pressure was lowered by both active treatments (Reiner et al. 1985). In the third study in 48 children with fever and/or pain of various origin, patients received either nimesulide 100mg suppositories or paracetamol 200mg suppositories 1 to 4 times daily. Nimesulide was associated with a significantly greater reduction in fever (fig. 5). Spontaneous pain was reduced somewhat quicker and to a greater extent by paracetamol, although nimesulide appeared to be longer acting. There were no significant differences in overall efficacy between groups (data on file, Helsinn).

3.8 Phlebitis and Thrombosis

In 20 patients with varicophlebitis and/or deep vein thrombosis, equal numbers of patients received either nimesulide 100mg twice daily or *Serratia* peptidase 5mg 3 times daily for 10 days. Nimesulide effectively reduced pain and local inflammation to a greater extent than *Serratia* peptidase (78 vs 33% at 5 days; 100 vs 85% at 10 days, respectively) [Agrifoglio 1986]. In a similar comparative study, 60 patients with acute inflammatory venous pathology of the lower limbs were randomised to receive either nimesulide 100mg twice daily or *Serratia* peptidase 5mg 3 times daily for 10 days. Local hyperthermia, cutaneous reddening, spontaneous pain and pain on movement were present in all patients. Good to complete resolution of these symptoms occurred in 86.7, 86.7, 93.4 and 80% of patients after 5 days of nimesulide, and in 96.7, 96.7, 93.4 and 93.4% after 10 days, respectively. Significantly lower efficacy was achieved with *Serratia* peptidase with respective improvements in symptoms being 36.7, 36.7, 46.7 and 36.7% on day 5, and 70, 63.4, 80 and 60% on day 10. Global physician evaluation ranked nimesulide treatment excellent in 50% and good in 50% compared with excellent in 7% and good in 86% with *Serratia* peptidase.

40 patients with venous leg ulcers were randomised to receive their normal treatment (no details given) and either nimesulide 100mg twice daily or no additional therapy. By final assessment, pain had been eliminated in 95 and 65% of patients, respectively. Disappearance of periulcerous dermatitis and hypodermatitis was also noted in 90 and 65%, respectively. Other symptoms which showed a greater degree of improvement with nimesulide included osteoendonal changes and perilesional oedema (Mancini et al. 1987).

3.9 Genitourinary Tract Inflammation

A 20-day double-blind parallel group study in 40 patients with acute infectious inflammation of the urogenital tract compared the efficacy of antibiotics (ampicillin 500mg 3 or 4 times daily or co-

trimoxazole 480mg 2 or 3 times daily) plus placebo with antibiotics plus nimesulide 100mg twice daily. The combination of antibiotic and nimesulide therapy produced a significantly greater and more rapid improvement in almost every symptom (prostate swelling, redness, oedema, compulsion, nocturia, body temperature). After 7 days, the mean severity of symptoms had decreased by 50% in the nimesulide group. There was also a concomitant reduction in raised erythrocyte sedimentation rate and white blood cell count, but not in other laboratory parameters (Pfändner 1984).

In 41 women with a variety of inflammatory genital tract diseases nimesulide 100mg twice daily or placebo were each given for 2 cycles of 15 days with a 15-day treatment-free period between. Nimesulide was associated with significant reductions in leucoxanthorrhoea, inflammatory vaginal secretions, adnexal swelling, dyspareunia and spontaneous or examination pain (Chiantera & DiLeo 1986).

In 32 patients with painful postoperative genitourinary inflammation nimesulide 100mg twice daily was compared with benzydamine 150mg daily over 8 days. In a second study (reported in the same paper), nimesulide 200 to 400mg was compared with placebo in a similar group of 33 patients, who were also receiving antibiotics. Nimesulide was more rapidly acting and gave superior clinical relief over the first 3 days than benzydamine, but thereafter there were no differences between groups. Compared with placebo, nimesulide was markedly superior, with resolution of symptoms in 9 and 42% of patients at 7 days, respectively (La Pera et al. 1986).

3.10 Post-Traumatic Inflammation

In 36 patients with recent traumatic distortion of the wrist, knee or tibiotarsal joint, inflammation and pain were treated with nimesulide 100mg twice daily or *Serratia* peptidase 10mg 3 times daily for 5 days. Both drugs significantly reduced swelling with complete disappearance in 13 and 9 patients, respectively, at the end of treatment. Of the other clinical symptoms measured, significant advan-

Table VIII. Summary of adverse effect data from clinical studies with nimesulide

Reference	No. of pts	Disease treated	Daily dose (mg)	Incidence of side effects (%)	Type of side effect	Comparison with other treatment
Allegra (1986)	53	RTI	200	7	Heartburn	
Bernasconi & Massera (1985)	19	Influenza	200	5	Heartburn	30% Aspirin + vitamin C
Data on file, Helsinn	14	Fever	100	7	Perspiration	0% Paracetamol
Emami Nouri (1984)	25	RTI	200	0		
Emami Nouri (1986)	27	ENT	200	0		8% Naproxen
Finiguerra et al. (1986)	40	RTI	200	7.5	Epigastric pain	
Gamarski (1981)	20	Arthritic conditions	200	30	Gastric disturbances	10% Placebo
La Pera et al. (1986)	33	Urogenital	200-400	8.5	Gastralgia Heartburn	6.5% Placebo 0% Benzydamine
Merchan et al. (1982)	10	Arthritis	200	0		
Milvio (1984a)	26	ENT	200	4	Heartburn	46% Benzydamine
Milvio (1984b)	25	Influenza	400	0		12% Aspirin
Milvio (1986)	22	RTI	200	9	Gastralgia	36% Aspirin + vitamin C
Moggian et al. (1986)	40	Dysmenorrhoea	100-200	5	Heartburn	
Ottaviani (1986)	67	ENT	200	<5	Heartburn	
Reiner (1982)	11	OA	100-300	36	Skin rash Heartburn Urticaria Gastralgia	
Reiner & Magni (1982)	10	RA	400	20	Erythema Hyperexcitability	
Reiner et al. (1985)	29	Fever	200	10	Flushing Perspiration Hypotension	0% Placebo 17% Diclofenac
Resta et al. (1987)	18	ENT	200	11	Gastralgia Erythema	17% Phenylprenazone
Schmoekel et al. (1985)	26	Fever	400-600	16	Diarrhoea Sleep disorder	15% Paracetamol
Spadero & Mascaretti (1986)	22	Chronic inflammatory conditions	200-400	0		0% Placebo
Tommasini et al. (1986)	22	RTI	200	0		5% Placebo
Ventura et al. (1985)	20	OA	200-400	5	Gastralgia	

Abbreviations: RTI = respiratory tract infection; ENT = ear, nose and throat (otorhinolaryngological) infection; OA = osteoarthritis.

tages were seen with nimesulide in terms of full resumption of articular function, and resolution of spontaneous pain. Global opinion of efficacy, assessed by the physician, was ranked 'good to excellent' in 16 vs 5 patients, respectively (Memeo et al. 1987). In another study, treatment with nimesulide 100mg twice daily for 5 days of 10 elderly female patients with ankle or knee joint trauma brought about resolution of symptoms in all patients (Rocca & Montagnani 1987).

4. Side Effects

At present, there are no short or long term studies in large enough numbers of patients to adequately assess the overall or individual incidence of side effects with nimesulide. Similarly, prior to this review, there were no sources of cumulated side effect data, with the exception of one paper which summarises experience with nimesulide in Italy stating that the drug is well tolerated, with side effects occurring in 0 to 6% of patients - heartburn being the most common adverse effect (Ambrosini 1986).

Table VIII shows the cumulated results of many individual studies in small numbers of patients with a variety of diseases. The incidence of side effects has usually ranged from 0 to 10%. Heartburn, gastralgia and other gastrointestinal disturbances have been the most common unwanted effects. Occasionally excessive perspiration, flushing, hyperexcitability, skin rash, erythema and sleep disorders have been reported.

In the limited number of comparative studies with other treatments, nimesulide has been associated with a higher number of adverse effects than placebo (Gamarski 1981; Reiner et al. 1985), but apparently fewer than with naproxen (Emami Nouri 1986), diclofenac (Reiner et al. 1985), aspirin and vitamin C (Bernasconi & Massera 1985; Milvio 1985), aspirin (Milvio 1984b) or benzydamine (Milvio 1984a). Of the comparative active therapies, only paracetamol showed similar or possibly fewer adverse effects (data on file, Helsinn; Schmökel et al. 1985).

In a prospective multicentre study, the hepatic

effects of several non-steroidal anti-inflammatory drugs was assessed (data on file, Helsinn). Overall there was an unequivocal correlation between drug consumption and liver enzyme changes. Comparing the most commonly administered agents the order of decreasing hepatotoxicity was diclofenac > naproxen > piroxicam, ketoprofen, and nimesulide. There was a highly significant synergy between alcohol and liver damage caused by these drugs.

Many studies have, however, comprehensively assessed the effects of nimesulide on haemoreological and other laboratory parameters. Where initially raised, nimesulide has produced significant reductions in white blood cell count and erythrocyte sedimentation rates (Bernasconi & Massera 1985; Gamarski 1981; Milvio 1984a). All other routinely monitored laboratory values (haemoglobin, red blood cell count, platelet count, neutrophils, eosinophils, basophils, lymphocytes, monocytes, alkaline phosphatase, serum alanine and aspartate transferases, bilirubin, blood urea nitrogen, serum creatinine, fasting blood sugar and total serum protein) have not been clinically significantly altered (Bernasconi & Massera 1985; Emami Nouri 1984; Gamarski 1981; Milvio et al. 1983, 1984; Reiner & Magni 1982).

Nimesulide 100 or 200mg daily was associated with reduced platelet aggregation but did not affect clotting factors either in healthy volunteers or patients being treated with nicoumalone (acencoumarol) [data on file, Helsinn]. Similarly, in diabetics being treated with glibenclamide, nimesulide 200mg twice daily for 7 days had no significant effects on fasting blood sugar concentrations (data on file, Helsinn).

5. Dosage and Administration

Nimesulide is usually administered as tablets, suppositories or granules at a dosage of 100 to 200mg twice daily in the treatment of a wide variety of inflammatory conditions and in the treatment of postoperative pain states. The drug is contraindicated in patients in whom hypersensitivity has

occurred and in those with gastric ulcer or haemorrhage.

6. Place of Nimesulide in Therapy

Studies to date suggest that nimesulide is an effective anti-inflammatory and analgesic agent in the treatment of osteoarthritis, rheumatoid arthritis, some chronic respiratory tract inflammatory conditions, otorhinolaryngological inflammation, soft tissue and oral cavity inflammation, chronic genitourinary tract inflammation, as well as in several other conditions such as dysmenorrhoea and phlebitis/thrombosis. Nimesulide has also shown promise as an analgesic for relieving postoperative pain.

However, these studies are limited in number for most of the aforementioned conditions, and often lack adequate controls (drugs not considered as standard comparative agents) and reporting methods within their design. Nevertheless, where comparative agents have been used, nimesulide has almost invariably proven to be at least as efficacious (and in many cases more effective). Nimesulide has also generally been associated with a lower incidence of side effects than most comparative drugs. These have been the usual adverse effects associated with non-steroidal anti-inflammatory drugs. However, too few patients have been studied overall to draw firm conclusions regarding its tolerability or efficacy.

Thus, nimesulide offers another effective alternative in the treatment of a variety of inflammatory and pain conditions, although more well-controlled studies comparing its activity with other standard anti-inflammatory agents are needed.

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