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Review
Nimesulide: Some Pharmaceutical and Pharmacological Aspects—An Update

ANIL K. SINGLA, M. CHAWLA AND A. SINGH*

*Pharmaceutics Division, University Institute of Pharmaceutical Sciences, Punjab University, Chandigarh 160 014 and *Panacea Biotec Ltd, P.O. Lalru, Lalru, Punjab 140 501, India*

Abstract

Nimesulide, a non-steroidal anti-inflammatory drug (NSAID), is administered orally or rectally twice daily for a variety of inflammation and pain states. This is a unique NSAID, not only because of its chemical structure but also because of its specific affinity to inhibit cyclooxygenase-2 (COX-2), thus exerting milder effects on the gastrointestinal mucosa. Current data on selective COX-2 inhibitors suggest that they may have an efficacy similar to that of standard NSAIDs. Initial general clinical experience with selective COX-2 inhibitors appears to show that they are particularly promising in individuals at risk because of renal diseases, hypertension or congestive heart failure.

Various experimental models and clinical studies have demonstrated the anti-inflammatory efficacy of nimesulide. Nimesulide is superior, or at least comparable in efficacy, to other NSAIDs, but is better tolerated and has less potential for adverse reactions. Thus, selective COX-2 inhibitors should have anti-inflammatory effects devoid of side effects on the kidney and stomach. They may also demonstrate new important therapeutic benefits as anticancer agents as well as help prevention of premature labour and even retard the progression of Alzheimer's disease. No clinically significant drug interactions have been reported for nimesulide.

Not much has been reported about the pharmaceutical aspects of nimesulide. Its poor aqueous solubility poses bioavailability problems in-vivo. This could be overcome by the formation of inclusion complexes with β-cyclodextrin, as has been reported by various researchers. However, absence of any in-vivo data regarding the relative absorption of nimesulide from β-cyclodextrin complex compared with that from conventional formulations of the drug makes the use of such fast-releasing complexes rather questionable. Only a limited number of assay procedures (HPLC, spectrophotometric, spectrofluorimetric) for the determination of nimesulide and its metabolite in plasma/urine samples or in dosage forms have been reported in the literature.

The purpose of this review is to provide a concise overview of the pharmacological and pharmaceutical profile of nimesulide. Various investigations carried out recently are reported, although older references to research performed on nimesulide have also been included, where appropriate.

Clinically, non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed preparations. The development of acetylsalicylic acid by F. Hoffmann opened a new era in the treatment of rheumatoid arthritis and other sorts of analgesia. Salicylates were extensively used after their introduction, but gradually it was realized that they were not devoid of side effects. This led to the development and discovery of a host of other less toxic NSAIDs. Continued synthesis of newer agents, for

Correspondence: A. K. Singla, Pharmaceutics Division, University Institute of Pharmaceutical Sciences, Punjab University, Chandigarh 160 014, India.

evaluation as anti-inflammatory compounds, led to the discovery of the more potent cyclooxygenase-2 (COX-2) inhibitor, R-805, the synthesis of which has been described in the patent literature (Moore & Harrington 1974). The discovery of nimesulide, a selective COX-2 inhibitor, stimulated several laboratories to develop newer and more efficacious COX-2 inhibitors. Studies with recently introduced selective COX-2 compounds have demonstrated that these compounds retain the anti-inflammatory effects characteristic of NSAIDs with a marked increase in gastrointestinal tolerability, as compared with classical non-selective cyclooxygenase inhibitors. Some of the selective COX-2 inhibitors which are either used clinically or are in developmental stages are celecoxib (SC 58635), rofecoxib (MK 966), meloxicam, nimesulide, L 745 337, RS 570 67000, SC 58125, SC 299, etodolac, NS 398, DFU and DuP 697.

COX-2 is induced in the kidney in response to sodium depletion or in hyperfiltration states, in postsynaptic excitatory neurons in the brain after electroconvulsive stimulation, in ovary and uterus during ovulation and implantation, in intestinal epithelium after bacterial infection and in colon adenoma and carcinoma cells. As COX-2 appears to play an important role in pathologic processes other than pain and inflammation, ongoing research is investigating the potential utility of COX-2 selective inhibitors in conditions such as colonic polyposis, colorectal cancer and Alzheimer's disease (Lipsky 1999a, b).

One of the selective COX-2 inhibitors, SC 58635 (celecoxib), when administered for 7 days to human volunteers, was found to be an effective analgesic for moderate to severe pain after tooth extraction (Hubbard et al 1996). It provided no evidence of gastric damage when administered to human volunteers for 7 days (Lanza et al 1997a). Another compound, DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl sulfonyl)-phenyl-2-(5 *H*)-furanone), was 100 times less potent than meloxicam or nimesulide in inhibiting microsomal cyclooxygenase-1 (COX-1) but was less ulcerogenic than either of the two drugs (Riendeau et al 1997). A derivative of DFU, MK 966 (rofecoxib), is available for the treatment of rheumatoid arthritis and osteoarthritis. When administered daily at a dose of 250 mg (for 7 days at 10 times its anti-inflammatory dose), MK 966 did not produce any incidence of gastrointestinal damage (Lanza et al 1997b).

A number of reviews (Biscarini et al 1988; Ward & Brogden 1988; Davis & Brogden 1994; Rabasseda 1996) have appeared regarding the pharmacological aspects of nimesulide.

Physicochemical Properties

Nimesulide, an acidic NSAID, differs from many such compounds in that it is acidic by virtue of a sulphonanilide rather than a carboxylic group (Figure 1). The first report on the preparation and anti-inflammatory properties of nimesulide appeared in 1975 (Grant et al 1975). It showed high anti-inflammatory, antipyretic and analgesic activity in addition to low toxicity, moderate incidence of gastric side effects and a high therapeutic index (Biscarini et al 1988).

Chemically, it is 4-nitro-methanesulphonanilide (MW 308), with a pKa of 6·4–6·8 (Rufer et al 1982; Magni 1991; Fallavena & Schapovral 1997; Piel et al 1997; Singh et al 1999) and a melting point of 147–148°C. Nimesulide is a yellowish crystalline powder which is soluble in acetone, chloroform and ethyl acetate, slightly soluble in ethanol and virtually insoluble in aqueous systems (solubility 0·01 mg mL^{-1}; Piel et al 1997). The very poor aqueous solubility and wettability of the drug gives rise to difficulties in the pharmaceutical formulation of oral or injectable solutions, and leads to a variable bioavailability. Studies have been carried out to increase the aqueous solubility of nimesulide by incorporating it within a nimesulide–L-lysine–β-cyclodextrin complex (Piel et al 1997) which increased its water solubility by a factor of 10 at pH 1·5 (0·050 mg mL^{-1} for the complex versus 0·005 mg mL^{-1} for the drug), a factor of 160 at pH 6·80 (2·373 mg mL^{-1} versus 0·015 mg mL^{-1} for drug) and a factor of 3600 in purified water (36 400 mg mL^{-1} for the complex versus 0·01 mg mL^{-1}). Other researchers (Barbato et al 1997; Vavia & Adhage 1999) have also carried out complexation studies of nimesulide with β-cyclodextrin, resulting in enhanced solubility. However, Jouzeau et al (1997) observed that the gastric safety of nimesulide was dependent on the drug concentration achieved in the gastric mucosa. Thus, enhanced solubility of the drug from β-cyclodextrin complex could result in an increased gastric irritation due to an elevated local drug concentration.

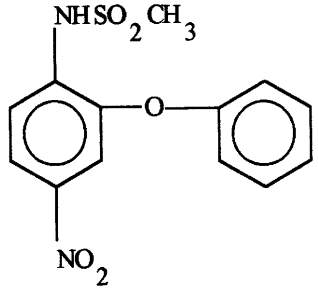

Figure 1. Chemical structure of nimesulide.

The lack of in-vivo data indicates lesser gastrointestinal irritation, and makes the use of nimesulide–β-cyclodextrin complex rather speculative. It is also difficult to understand how the improved solubility of the complex will be of any benefit as the majority of the formulations available are designed for rapid absorption from the upper part of the gastrointestinal tract. An enhanced dissolution of nimesulide from crystals prepared by solvent change (ethanol–water, 1 : 1) in the presence of Tween 80 (1%) has been reported by Kapoor et al (1998).

Pharmacology

The anti-inflammatory, analgesic and antipyretic activity of nimesulide have been studied in a number of experimental models and in numerous clinical trials. Swingle et al (1976) demonstrated the anti-inflammatory activity of nimesulide by conventional methods (carrageenan-induced paw oedema, UV-induced guinea-pig skin erythema and adjuvant-induced arthritis of the rat). Calculation of acute therapeutic indices (LD50-lethal dose in 50% animals/ED50-effective in dose in 50% animals) for 8 acidic drugs showed nimesulide to possess a more favourable index (Table 1).

Pharmacodynamic properties

Effect on cyclooxygenase activity. Tissue injury is associated with the release of numerous inflammatory mediators including prostaglandins. Prostaglandins derived from the arachidonic acid cascade are implicated in the production of inflammatory pain and in sensitising nociceptors to the action of other mediators. They are synthesised from arachidonic acid via the endoperoxide biosynthetic pathway, the initial step of which is catalysed by the enzyme cyclooxygenase (COX, PGHS).

Table 1. Acute oral therapeutic indices of NSAIDs in rats.

Drug	ED50 ($mg\,kg^{-1}$)[a]	LD50 ($mg\,kg^{-1}$)[b]	Therapeutic index
Nimesulide	1·25	324 (295–356)	260
Naproxen	2·1	395 (281–557)	190
Ibuprofen	13·5	923 (833–1020)	68
Diflumidone	38	750 (694–811)	20
Flufenamic acid	14·7	249 (221–280)	17
Phenylbutazone	29·5	406 (375–440)	14
Acetylsalicylic acid	135	1520 (1360–1710)	11
Indomethacin	2·95	21 (19–23)	7

Swingle et al 1976. [a]Calculated in carrageenan-induced rat paw oedema from the 3-point regression of response on dose. [b]Calculated by the method of Litchfield & Wilcoxon (95% confidence limits are given in parentheses).

Two forms of COX (COX-1 and COX-2) have been characterized. COX-1 is important in circumstances where prostaglandins have a protective effect, such as gastric mucus production and renal blood-flow maintenance. COX-2, the inducible form of the enzyme, is the major form of the isozyme associated with inflammation. COX-2 is induced in endothelial cells, macrophages and synovial fibroblasts by inflammatory agents. The ratio of inhibition of COX-1 to COX-2 by a NSAID determines the likelihood of adverse effects. The challenge must be to develop drugs selective for the inducible form of the enzyme (Cashman & McAnulty 1995).

In a study with COX-2 and COX-1 isolated from ram seminal vesicles and sheep placenta, nimesulide has been shown to selectively inhibit COX-2 without affecting COX-1 activity (Vago et al 1995). The inhibition of COX-2 was characterized by time dependence, so the IC50 (inhibitory concentration in 50% animals) value varied according to the time of incubation (from $70 \pm 35\,\mu mol\,L^{-1}$ to $0{\cdot}07 \pm 0{\cdot}05\,\mu mol\,L^{-1}$). Nimesulide did not affect COX-1 activity until a concentration of $1\,\mu mol\,L^{-1}$ was attained, and with an $IC50 > 100\,\mu mol\,L^{-1}$. It was concluded that nimesulide's selective inhibitory effect on COX-2 was time dependent whereas its weak inhibitory effect on COX-1 was not. Famaey (1997) observed that the inhibitory ratio of nimesulide for COX-2/COX-1 varied according to the assay procedure over the range 0·7600–0·0004 (i.e. a 1·3–2512-fold higher selectivity for COX-2 than COX-1). However, it has recently been reported (Hawkey 1999) that nimesulide may not be selective for COX-2 because the doses used in practice result in plasma concentrations at which COX-2 selectivity is lost.

The anti-inflammatory activity of drugs selective for the inhibition of COX isoforms in rat carrageenan-induced pleurisy were evaluated by Gilroy et al (1998a). Suppression of inflammation by COX-2 selective inhibitors, NS 398 (*N*-[2-cyclohexyloxy]-4-nitrophenyl methanesulphonamide) and nimesulide, and by piroxicam and aspirin more selective for COX-1, was measured. Piroxicam and aspirin were found to significantly inhibit inflammatory-cell reflux, exudate and prostaglandin E_2 formation 6 h after carrageenan injection. In contrast, at 3 h after carrageenan injection, COX-2 inhibitors significantly inhibited all the parameters of inflammation. However, suppression with piroxicam and aspirin was greater and more pronounced than at 6 h. COX-2 inhibitor dosing did not decrease thromboxane B_2 production from platelets isolated from rats with carrageenan-induced pleurisy, thereby demonstrating that at the

doses used, COX-2 inhibitors did not inhibit COX-1, as platelets contain only this isoform. In another study, Panara et al (1998) incubated heparinized blood samples from healthy subjects with lipopolysaccharide ($10\,\mu g\,mL^{-1}$) for 24 h at 37°C. Prostaglandin E_2 was measured in plasma as an index of monocyte PGHS-2 activity. Further, whole blood was allowed to clot at 37°C for 60 min and the production of thromboxane B_2 assessed as an index of platelet PGHS activity. Nimesulide was found to be a potent inhibitor of human monocyte PGHS-2. Despite a 20-fold selectivity ratio for PGHS-2, therapeutic plasma levels of nimesulide were sufficiently high to cause detectable inhibition of platelet PGHS-1. However, Young et al (1996) observed nimesulide to have only a 4-fold greater selectivity for PGHS-2 than PGHS-1. In another study (Harada et al 1998), indomethacin was observed to inhibit PGHS-1 and PGHS-2 almost equally while nimesulide only inhibited PGHS-2 in rats ($3\,mg\,kg^{-1}$ each). Table 2 summarises the activity of nimesulide and representative NSAIDs against COX-2 and COX-1. Nakatsugi et al (1996a) observed nimesulide to strongly inhibit lipopolysaccharide-induced prostaglandin E_2 production without any effect on COX-2 protein expression, suggesting a possible role of the drug in inhibiting the ability of COX-2 to convert arachidonic acid endogenously released in response to lipopolysaccharide stimulation.

Table 2. Comparative activity of various NSAIDs against COX-2/COX-1.

Drug	COX-2/COX-1 ratio
Nonselective COX-2 inhibitors	
Piroxicam	600
Tolmetin	175
Aspirin	166
Sulindac	100
Indomethacin	60
Tolfenamic acid	16·7
Ibuprofen	15
Paracetamol	7·4
Sodium salicylate	2·8
Flurbiprofen	1·3
Carprofen	1·0
Diclofenac	0·7
Naproxen	0·6
Selective COX-2 inhibitors	
Meloxicam	0·8
Nimesulide	0·1
Etodolac	0·1
SC 58125	0·007
NS 398	0·006
L 745 337	0·004
Celecoxib	0·003
DFU	$<0{\cdot}001$

Data corresponds to the potency ratios against COX-2/COX-1 in intact cell systems (Vane & Botting 1996, 1998).

Taniguchi et al (1997) investigated the antipyretic activity of nimesulide in yeast-induced febrile rats. Yeast-injected rats were found to develop marked fever and exhibited an approximately 7-fold increase in the brain levels of prostaglandin $E_{2\alpha}$ and an approximately 2-fold increase in the expression of COX-1 mRNA. Nimesulide produced a dose-dependent antipyretic action, which was stronger than that of indomethacin and ibuprofen. An increase in brain prostaglandin E_2 levels was observed with a decreasing dose of nimesulide whereas the expression of COX-2 mRNA was not affected. Nimesulide markedly inhibited the enhanced brain COX activity, primarily COX-2, in-vivo and increased the COX activity in-vitro in a dose-dependent manner. These results suggested that the antipyretic action of nimesulide was primarily mediated through the selective inhibition of the activity of brain COX-2 induced under febrile conditions.

Pelletier et al (1997) evaluated the effects of therapeutic and pharmacological concentrations of nimesulide and naproxen on the synthesis of urokinase, plasminogen activator inhibitor (PAI-1) and interleukin-6 (IL-6) in human synovial fibroblasts isolated from osteoarthritis patients and were found to induce a dose-dependent decrease in urokinase synthesis. Both nimesulide and naproxen exerted a stimulatory effect on the synthesis of PAI-1 and an inhibitory effect on the synthesis of IL-6. These effects could have a positive impact on the balance of plasminogen activator/inhibitor, which could help to decrease cartilage catabolism. The effect of nimesulide on patellar cartilage and bone content was also investigated by Gilroy et al (1998b) in a model of *Mycobacterium tuberculosis*-induced monoarticular arthritis in the rat and its protective and destructive effects were compared with those of piroxicam. Piroxicam ($10\,mg\,kg^{-1}$) and nimesulide ($5{\cdot}0\,mg\,kg^{-1}$) significantly exacerbated *M. tuberculosis*-induced glycosaminoglycans loss but did not alter *M. tuberculosis*-induced patellar bone loss but both the drugs resulted in a reduction in patellar joint swelling. The selective inhibition of COX-2 was thus thought to have resulted in the amelioration of synovitis with a lowered risk of NSAID-induced cartilage damage in rheumatic conditions.

Effect on neutrophil functions and free radical generation. Nimesulide not only inhibits prostaglandin synthesis in certain cell types but also has pleiotropic effect on neutrophil functions, including the respiratory burst, integrin-mediated adherence and synthesis of platelet-activating factor (PAF). The effect of nimesulide on PAF synthesis was compared with its effect on the production of

leukotriene B_4 (LTB_4) and was found to dose-dependently inhibit both processes in neutrophils stimulated with serum-treated zymosan with a comparable efficacy (IC50: $10-20\,\mu mol\,L^{-1}$). In formyl-methionyl-leucyl-phenylalanine (fMLP)-stimulated neutrophils (treated with cytochalasin B), IC50 values were observed to be 30 and $50\,\mu mol\,L^{-1}$ for PAF and LTB_4 synthesis, respectively. These results indicated an inhibition of a common step in the release of the mediators (i.e. the activation of phospholipase A2), possibly by elevation of intracellular cAMP. The inhibitory effects of nimesulide on PAF and LTB_4 production could largely be prevented by the addition of H89, an inhibitor of cAMP dependent protein kinase. It was thus concluded that an increase in intracellular cAMP was instrumental in the observed effects of nimesulide in the release of PAF and LTB_4 by activated neutrophils and that the limited availability of arachidonic acid might have contributed to the effects of nimesulide on prostaglandin synthesis as observed in other cell types (Tool & Verhoeven 1995). Dallegri et al (1992a, b) investigated the effects of nimesulide on the ability of neutrophils to oxidatively inactivate α-1 proteinase inhibitor (A1PI). It was observed that nimesulide prevented the inactivation of A1PI by effectively scavenging the HClO released by the neutrophils. It was suggested that the anti-inflammatory effect of nimesulide could have been due, at least in part, to the rescue of A1PI from the neutrophil oxidative attack. The rescue of A1PI may alter the elastase-A1PI balance in favour of the inhibitor, with resulting tissue protection. Upon being recruited to tissue sites and exposed to phagocytic targets, neutrophils release oxidants which may cause the inactivation of A1PI. Consequently, the ability of A1PI to inhibit the proteolytic activity of elastase (released by neutrophils as a result of leakage from phagocytic vacuoles) is diminished. Nimesulide is efficient at limiting the extracellular availability of HClO surrounding neutrophils and thus prevents the inactivation of A1PI by neutrophils. It was reported by Capsoni et al (1987) that oxygen-derived free-radical release from activated neutrophils may be in part responsible for tissue damage in the acute phase of inflammation. Nimesulide inhibited the respiratory burst of phagocytosing neutrophils without affecting their phagocytic or chemotactic responsiveness. In fact, chemiluminiscence and superoxide ion ($-OO$) generation by polymorphonuclear leukocytes stimulated with zymosan particles or with the synthetic peptide fMLP were inhibited by nimesulide and 4-hydroxy nimesulide in a dose-dependent fashion without affecting cell viability.

Dapino et al (1994) observed that a reduction in neutrophil transepithelial migration occurred as a result of nimesulide challenge, primarily due to limiting cell anchorage to tumour necrosis factor-α (TNF_α)-activated endothelium. Thus, nimesulide was thought to have a potential to downregulate neutrophil extravasation and in turn, the burden of neutrophil oxidants and protease, which are responsible for tissue injury at the site of inflammation. The effect of nimesulide on the elevation of TNFα levels in plasma has also been investigated by Azab et al (1998). Male Sprague-Dawley rats were injected with *Escherichia coli* lipopolysaccharide ($1\,mg\,kg^{-1}$, i.p.) resulting in a dramatic increase in plasma TNFα levels 60 min after administration ($3890 \pm 280\,pg\,mL^{-1}$ compared with undetectable levels in the control). Nimesulide ($30\,mg\,kg^{-1}$) administered 60 min before lipopolysaccharide (LPS), prevented LPS-induced elevation in TNFα levels in plasma, whereas the circulating levels of TNFα were unaltered by nimesulide alone. Thus, the anti-inflammatory properties of nimesulide were partly attributed to its ability to inhibit the effects of TNFα production. The results suggest that nimesulide is endowed with a high potential to efficiently control the harmful effects of oxidants produced by neutrophils at inflammatory tissue sites.

Nimesulide was also observed to inhibit the activity of PAF and LTC_4 in activated eosinophils and was found to be an inhibitor of the chemotactic response of human eosinophils (Tool et al 1996).

Bevilacqua et al (1994) observed that nimesulide decreased the production of superoxide anion ($-OO$) in fMLP- or phorbol myristate acetate (PMA)-stimulated polymorphonuclear leukocytes in a dose-dependent manner. The inhibition of $-OO$ was thought to be possibly related to its inhibitory effect on polymorphonuclear leukocyte cytosolic phosphodiesterase (PDE) type IV (IC50: $39 \pm 2\,\mu mol\,L^{-1}$), to the related increase in cAMP ($P < 0{\cdot}01$ at $1{\cdot}0\,\mu M$) and the subsequent increase in protein kinase A (PKA) activity. The activation of PKA might promote the phosphorylation of a number of substrates, thus inhibiting the assembly of NADPH-oxidase in the plasma membrane. Accordingly, nimesulide decreased PMA-induced assembly of NADPH oxidase in the polymorphonuclear leukocyte plasma membrane by about 35%. PKA activation may have also interfered with chemotaxis. The inhibition of PDE IV may explain many of the effects of nimesulide. Oral administration of nimesulide was also found to lower the phagocytic ability to generate $-OO$ in response to both fMLP (% inhibition: 67·62) and opsonized zymosan (% inhibition: 36·75). Lactoferrin release

by neutrophils was unaffected, proving that the drug did not affect exocytosis of specific granules (Ottonello et al 1992). The ability of nimesulide to inhibit the oxidative burst was also proposed by Capecchi et al (1993), who studied the effect of the drug on human polymorphonuclear leukocyte functions such as free-radical generation and enzyme release and on cytosolic free calcium levels following activation with specific stimuli, in-vitro. Nimesulide ($1-50\,\mu mol\,L^{-1}$) showed a dose-dependent inhibitory activity on $-OO$ and chemiluminescence production from polymorphonuclear leukocytes stimulated with the oligopeptide fMLP, the ionophore A23187 and the phorbol ester PMA. Studies with the fluorescent calcium chelating dye, FORA2/AM, showed the ability of nimesulide to reduce free cytosolic calcium, the production of which was increased as a result of fMLP and the ionophore, ionomycin. Pre-incubation of the cells with theophylline significantly counteracted the inhibitory activity of nimesulide both on free-radical production and enzyme release and on the free cytosolic calcium increase sustained by fMLP and ionophores. The free-radical and hydroxyl scavenging activity of nimesulide have also been reported by Facino et al (1995) who observed a specific hydroxyl-radical-scavenging activity of nimesulide, which was able to prevent and limit the free-
radical-mediated tissue damage in both acute and chronic inflammatory situations. De Mello et al (1994) demonstrated that nimesulide-exposed peripheral neutrophils from healthy subjects produced significantly less superoxide when challenged by PMA ($50\,ng\,mL^{-1}$) and opsonized zymosan ($1\,mg\,mL^{-1}$). Nimesulide effectively decreased the PMN chemotaxis when challenged by leukotriene and fMLP.

Effect on histamine release. It has been proposed that nimesulide and its primary metabolite, 4-hydroxy nimesulide, (Casolaro et al 1993) reverse the enhancement of IgE-mediated histamine release from basophils by acetylsalicylic acid and indomethacin. In a study involving the investigation of the effects of nimesulide and 4-hydroxy nimesulide on the release of preformed histamine and de-novo synthesised mediators (sulphidopeptide, LTC_4 and prostaglandin D_2) from human basophils and mast cells isolated from lung parenchyma (HLMC) and skin cells (HSMC), nimesulide and 4-hydroxy nimesulide ($10^{-6}-10^{-3}$ M) were observed to cause a concentration-dependent inhibition (2·9–60% and $3{\cdot}7 \sim 90\%$, respectively) of IgE-mediated histamine release from basophils. Nimesulide markedly inhibited the de-novo synthesis of LTC_4 from basophils, LTC_4 and prostaglandin D_2 from HLMC and prostaglandin D_2 from HSMC. The inhibitory effect of adenylate cyclase agonist on prostaglandin E_1 and forskolin was potentiated by the drug and its metabolite. Antihistaminic activity of nimesulide has also been studied by Berti et al (1990). Nimesulide inhibited the immune release of histamine, the activity being specific for H_1 receptors as was demonstrated on isolated strips of guinea-pig trachea and on histamine-induced multiphasic ionotropic response in the left atria of guinea-pig. The effect was noncompetitive and nimesulide ($1{\cdot}6\,\mu mol\,L^{-1}$, i.v.) inhibited both bronchoconstriction (69%) and TXB_2 formation (93%) induced by histamine ($0{\cdot}05\ \mu mol\,kg^{-1}$, i.v.) in anaesthetised guinea-pig.

Effect on complement activity. Auteri et al (1988) observed that nimesulide blocked immunohaemolysis in-vitro and had a direct effect on serum complement activity. The activation of third complement was blocked by nimesulide.

Gastric effects. In the stomach, COX-1 is responsible for the production of cytoprotective prostaglandins whereas small quantities of COX-2 are also expressed constitutively (Kargman et al 1996). In the upper part of the gastrointestinal tract, prostaglandins have a cytoprotective role, as was evidenced from studies in which prostaglandin analogues reduced gross gastric damage induced by bile salts, strong acid or bases, thermal injury, ethanol or NSAIDs (Whittle 1976; Robert et al 1979; Miller 1983). This protection could have been due to a reduction in gastric acid secretion, maintenance of mucosal blood flow, stimulation of mucus and bicarbonate secretion and maintenance of mucosal integrity (Whittle 1976; Cryer & Feldman 1992; Wallace 1992). Recent studies by Kargman et al (1996) have indicated no detectable COX-2 protein activity in the stomach, small intestine and colon of a variety of animals and humans, while abundant COX-1 activity and protein were observed. Thus the therapeutic use of selective COX-2 inhibitors should have few gastric effects. However, there is still some speculation regarding the utility of selective COX-2 inhibitors. For example, estimates of the selectivity of COX-2 inhibitors based on in-vitro studies are likely to be poor predictors of selectivity in-vivo. Efficacy with selective blockade of COX-2 may be inferior to that achieved with the combined inhibition of COX-1 and COX-2. Furthermore, in situations of gastrointestinal ulceration, COX-2 is responsible for the production of prostaglandins that are essential for repair. Under these circumstances, inhibi-

tion of COX-2 may result in a delay in the healing of the ulcers and exacerbation of inflammation. It is necessary, therefore, to exercise some restraint before the theory is fully accepted that COX-2 inhibitors are effective anti-inflammatory drugs that spare the gastrointestinal tract from injury (Wallace et al 1998). This was corroborated by Schmassmann et al (1998) who observed an accumulation of COX-2 in monocytes, macrophages, fibroblasts and endothelial cells after gastric ulceration. Selective inhibition of COX-2 by L 745 337, in a potentially therapeutic range, resulted in an impairment of ulcer healing. Similar results were reported by Gretzer et al (1998), who observed that treatment with selective COX-2 inhibitors significantly delayed healing in chronic experimental ulcers in rats and mice. They further reported that COX-2 formation was induced in gastric mucosa during ulceration, thereby suggesting a possible role for COX-2-derived prostaglandins in the healing process. Thus, it was concluded that though COX-2 inhibitors did not produce any gastric mucosal lesions, they did abolish the protective activity of a mild irritant.

Laudanno et al (1998) investigated COX-1 and COX-2 selectivity of 16 NSAIDs at ulcerogenic doses in two experimental models wherein the drugs were given either subcutaneously after solid food for antrum ulcers and intestinal erosions or orally for fundic and intestinal erosions. Following subcutaneous administration, slight intestinal erosions were observed ($0-23\,mm^2$, $P < 0{\cdot}01$) with a conspicuous absence of ulcers. The administration of drugs by orogastric tubing yielded 0–5% fundic erosions and 0–22-mm^2 intestinal erosions. Nakatsugi et al (1996b) observed that nimesulide did not produce stress-induced gastric lesions even at 30 times the anti-inflammatory dose. In a study (Nakatsugi et al 1996a) involving rats, carrageenan was injected intrapleurally with a subsequent increase in prostaglandin E_2 production and induction of newly synthesised COX-2 in the pleural exudate cells without any effect on COX-1 levels. Nimesulide was able to reduce pleural prostaglandin E_2 production and was almost as active as indomethacin and 10 times more active than ibuprofen. Contrary to the effect of nimesulide, a decrease in the gastric prostaglandin E_2 production induced by indomethacin and ibuprofen resulted in stress-induced gastric lesions even at anti-inflammatory doses.

The effect of nimesulide on duodenal bicarbonate (HCO_3^-) secretory and ulcerogenic responses to mucosal acidification were compared with that of indomethacin by Hirata et al (1997) in rats. Duodenal HCO_3^- secretion in anaesthetised rats was increased in response to mucosal acidification. The increased HCO_3^- response to the acid was suppressed by pretreatment with indomethacin ($10\,mg\,kg^{-1}$, s.c.), while nimesulide ($10\,mg\,kg^{-1}$, s.c.) had no effect. The luminal release of prostaglandin E_2 was found to increase during and after mucosal acidification and this response was inhibited by indomethacin but not by nimesulide. Indomethacin was observed to provoke haemorrhagic lesions in the duodenum when acid hypersecretion was concomitantly induced by histamine ($8\,mg\,kg^{-1}\,h^{-1}$, i.v.) whereas nimesulide did not cause any damage and had no effect on histamine-induced acid secretion. However, it was reported by Davis & Brogden (1994) that symptomatic tolerability of nimesulide is not superior to other NSAIDs and one epidemiological study suggested that ulcer complications are as common with nimesulide as with other NSAIDs (Rodriguez et al 1998).

Effect on myometrium. Both COX-1 and -2 are expressed in the uterine epithelium at different times and may have a role to play in the implantation of the ovum and the angiogenic process of placenta formation (Chakraborty et al 1996). Gibb & Sun (1996) observed elevated levels of COX-2 mRNA immediately before and after the start of labour. Preterm labour can be caused by an intrauterine infection resulting in the release of endogenous factors that increase prostaglandin production following COX-2 upregulation (Spaziani et al 1996). Selective inhibitors of COX-2 have been shown to reduce prostaglandin synthesis in isolated foetal membranes and could prove useful in delaying premature labour without the adverse effects of classical NSAIDs (Sawdy et al 1997).

In one of the first studies on the effect of nimesulide on isolated rat myometrium (Malofiejew & Blaszkiewicz 1979), nimesulide was observed to reduce and eliminate contractile activity. It was proposed that nimesulide weakened and abolished the reaction of the rat myometrium to polypeptides (oxytocin, vasopressin, bradykinin and hypertensin). Exogenous prostaglandin $F_{2\alpha}$ ($10^{-7}-10^{-6}\,g$) was able to restore myometrial reactivity to the polypeptides in the presence of nimesulide, but did not alter the myometrial reactivity to Ca^{2+}, Ba^{2+} or K^+ ions. The ability of nimesulide to affect myometrial contractility and voltage-gated Ca^{2+}-channel current has been recently investigated by Sawdy et al (1998) in tissue stripe and isolated human myometrial smooth-muscle cells from myometrial biopsies from women undergoing caesarian section at term. Nimesulide ($100\,\mu M$) was found to com-

pletely inhibit myometrial contraction. The Ca^{2+}-channel current was inhibited in a concentration-dependent manner with a 40% reduction of the current at 100 μM nimesulide, which also accelerated the decay of the Ca^{2+}-channel current. The inhibition of the Ca^{2+}-channel current was unaffected by the presence of either prostaglandin $F_{2\alpha}$ or prostaglandin E_2 (30 μM) and was of similar magnitude, whether 10 mM Ba^{2+} or 1·5 mM Ca^{2+} was used as the charge carrier. The concentration of nimesulide required to suppress spontaneous contractility in pregnant human myometrium was much higher than that necessary to inhibit prostaglandin production. This led to the conclusion that nimesulide inhibited myometrial contractility via mechanisms independent of COX inhibition, and that this could have been due to the blockade of the Ca^{2+}-channel current. In a related study, Beguma-Nibasheka & Nathanielsz (1998) tested the effects of administration of nimesulide to ovariectomised non-pregnant sheep subsequent to in-vitro myometrial responsiveness to prostaglandin E_2, prostaglandin $E_{2\alpha}$ and oxytocin. Nimesulide lowered spontaneous myometrial contractility and sensitivity to oxytocin while increasing the sensitivity to prostaglandins, indicating a down-regulation of oxytocin receptors and an upregulation of prostaglandin receptors or intracellular signalling events. Both the treatments decreased the elevated uterine impedance in dysmenorrhoea to almost the normal level. Nimesulide induced a slightly faster and more complete decrease of uterine vascular resistance in dysmenorrhoea, towards normal eumenorrhoeic levels compared with naproxen. The ovarian branch remained unaffected, the most prominent changes being observed in the fundic region.

The effect of inhibiting prostaglandin production by an infusion of nimesulide, with a subsequent expression of labour-related genes in pregnant sheep, was investigated by Wu et al (1998). Foetal plasma prostaglandin E_2 levels decreased during nimesulide infusion ($P < 0{\cdot}05$), whereas oestrogen receptor (ER), oxytocin receptor (OTR), heat shock protein 70 (Hsp 70) and heat shock protein 90 (Hsp 90) mRNA increased during spontaneous term labour in vehicle-infused ewes in both the myometrium and endometrium. In the myometrium, after nimesulide infusion, OTR and Hsp 70 mRNA decreased significantly ($P < 0{\cdot}05$) compared with the vehicle-infused animals, but the changes in Hsp 90 mRNA fell outside the level of significance. Nimesulide reversed the upregulation of PGHS-2 mRNA that occurred in the myometrium, endometrium and the placenta during infusion of the vehicle ($P < 0{\cdot}05$). Inhibition of prostaglandin production resulted in decreased foetal plasma levels of prostaglandin E_2. Altered prostaglandin production following nimesulide administration could have resulted in a decreased abundance of mRNA for several of the well-described cassette of uteroplacental labour-related genes.

In a double-blind, placebo-controlled study (Pirhonen & Pulkkinen 1995), six eumenorrhoeic women were given either placebo or nimesulide (100 mg, single oral dose) during two consecutive cycles. Six women with moderate-to-severe dysmenorrhoea were treated with placebo, nimesulide or naproxen (500 mg, single oral dose) during 3 consecutive cycles. Uterine impedance (pulsatile index, PI) was measured during day 1 of the cycle at four different levels of the uterus and in the ovarian branch of the uterine artery. In eumenorrhoeic women, no significant changes were found with any of the treatments whereas in dysmenorrhoeic patients nimesulide relieved the symptoms and also decreased the uterine artery PI earlier than naproxen.

Hepatic effects. Six patients were reported to develop acute liver damage following administration of nimesulide (Steenbergen et al 1998). Four women developed acentrilobular ($n = 3$) or panlobular ($n = 1$) bridging necrosis, whereas 2 men showed a bland intrahepatic cholestasis. Jaundice was the presenting symptom in five of the six cases. One patient with hepatocellular necrosis and one with cholestasis had the hallmarks of hypersensitivity with an increased blood and tissue eosinophilia. One patient died from a pancreatic tumour 5 months after the diagnosis of toxic liver injury. In all other patients, the liver tests returned to normal levels within a late follow-up period of 6–17 months.

Renal effects. Renal prostaglandins are responsible for the regulation of several aspects of renal physiology, including renal blood flow and haemodynamics, renin secretion and tubular sodium and water reabsorption (Frazier & Yorio 1992; Navar et al 1996). Renal insufficiency, especially volume contraction, results in increased levels of renin, angiotensin and angiotensin II. The increased levels of angiotensin II in turn lead to increased renal prostaglandin production. In states of effective renal blood flow there is little stimulation of angiotensin II and, consequently, little synthesis of renal prostaglandins. Thus, administration of NSAIDs to healthy subjects with normal intravascular volume generally results in no compromise in renal function (Clive & Stoff 1984). However, where there is intravascular volume contraction, COX-2 synthesis

is induced, and renal haemodynamics are more dependent on the contribution from prostaglandins. Depending on the proportion of the overall prostaglandin pool that is contributed by COX-2 during intravascular volume depletion, it is understandable that selective COX-2 inhibitors could considerably compromise renal functions in such scenarios. This hypothesis is supported by the observation that genetically engineered COX-2-deficient mice develop severe nephropathy (Morham et al 1995). However, Cook et al (1997) have suggested that COX-2 is mainly localized in areas of the kidney that are not important to glomerular autoregulation and that the effect on the arterioles is mainly due to COX-1 activity.

Steinhauslin et al (1993) evaluated the effects of single and repeated doses of nimesulide on renal haemodynamics and electrolyte excretion in 8 healthy volunteers during a prolonged course of furosemide. Nimesulide was found to induce an acute but transient decrease in the indices of renal haemodynamics and appeared to have a sodium- and water-retaining effect. Its administration was also associated with weight gain and was characterized biologically by a decreased sodium and free water excretion in response to furosemide. The diuretic-induced renin activity was blunted by nimesulide. A resulting decrease in the aldosterone plasma level probably contributed to the decreased potassium secretion. However, in a study involving 16 healthy men (Warrington et al 1993), nimesulide (200–300 mg twice daily) was well tolerated. At a dose of 400 mg (twice daily), laboratory tests and urine analysis did not show any adverse effects. Serum creatinine concentrations were stable throughout the study, indicating that the glomerular filtration rate was unaffected by nimesulide therapy. The lack of nephrotoxicity of nimesulide was due to its weak inhibitory effect on renal COX in therapeutic doses. This is supported by the studies of Ceserani et al (1991), who observed that nimesulide did not significantly decrease urinary prostaglandin E_2 excretion in rats.

Dermatological effects. Four patients suffering from acute phases of Hallopeau's acrodermatitis were treated with nimesulide (200 mg daily) (Piraccini et al 1994). Improvements were achieved in inflammation signs and subjective pain within a few days. Prolonged treatment with nimesulide during remission phases prevented the relapse of dermatitis. Caputo et al (1996) observed marked improvements and restoration of finger motility in a 9-year-old boy suffering from parakeratosis, acanthosis with papillomatosis exocytosis and spongiosis, after the first month of nimesulide therapy (100 mg daily for 20 days followed by 50 mg daily for the next 20 days); the nail plates also reappeared because of the regression of eponychium.

Table 3. Percentage haemolysis as a function of 4-hydroxy nimesulide concentration.

4-Hydroxy nimesulide concn (μM)	% Haemolysis
Control	100
1·0	85·2 ± 3·4
5·0	63·5 ± 3·9
10·0	43·5 ± 6·3
20·0	14·5 ± 4·3

Values are expressed as mean ± s.d.

Effect on blood components. The protective effect of 4-hydroxy nimesulide on red blood cell haemolysis (0·2%, $3{\cdot}5 \times 10^7$ cells (mL blood)$^{-1}$) induced by cumene hydroperoxide (CuOOH, 50 μM) was evaluated (Facino et al 1997) by turbidimetric and morphological analysis. 4-Hydroxy nimesulide was found to inhibit CuOOH-induced haemolysis in a dose-dependent manner. The protective effect, calculated after 150 min incubation, started at 1 μmol which increased with increasing concentrations of hydroxy nimesulide (Table 3). In the samples protected with 10 and 20 μmol there was a significant delay (30 and 60 min) in the onset of haemolytic response. The efficacy of 4-hydroxy nimesulide was comparable with that of α-tocopherol in haemolysis experiments, and a cooperative interaction between
the two was observed (both at 10 μM) leading to the conclusion that 4-hydroxy nimesulide protected the red blood cell membrane by directly quenching the reactive oxygen species generated by the haemoglobin/peroxide interaction.

In a randomised, double-blind, placebo-controlled, parallel-group, single-centre study performed on 20 healthy male volunteers (Marbet et al 1998), bleeding times remained within the normal range after the administration of nimesulide (100 mg twice daily for 7 days).

Effect on reproductive tract and fertility. COX-2 appears to play an important role during ovulation, fertilisation, blastocyst uterine implantation and deciduation. It also has a role in normal oocyte maturation (Lim et al 1997). Thus, because of the apparent physiological importance of the enzyme, it becomes imperative to closely monitor the clinical manifestation of selective COX-2 inhibitors to ensure their safety.

Pharmacokinetics of Nimesulide

Numerous pharmacokinetic studies have been carried out on nimesulide following oral or rectal administration (Bernareggi 1993) in healthy volunteers, paediatric patients, patients with a predisposition for altered pharmacokinetics and in the elderly (Olive & Rey 1993).

Bernareggi (1998) reported that oral administration of nimesulide (100 mg, tablets/granules/suspension) in healthy human volunteers resulted in a rapid and extensive absorption with a C_{max} (2·86–6·5 mg L^{-1}) being reached within 1·22–2·75 h. The presence of food did not reduce either the rate or extent of drug absorption. Rectal administration produced a lower C_{max}, which occurred later than that after oral administration with bioavailability from suppositories ranging between 54–64% relative to the orally administered formulations. The drug was rapidly distributed with an apparent volume of distribution of 0·18–0·39 L kg^{-1} and was found to be extensively bound to albumin (up to 99%). The mean terminal half-life varied between 1·8 and 4·73 h. Nimesulide was largely eliminated via metabolic transformation, with the major metabolite being 4-hydroxy nimesulide, whereas minor metabolites have also been detected in the urine and faeces in a conjugated form. The total plasma clearance of nimesulide was 31·02–106·16 mL h^{-1} kg^{-1}. A steady-state drug concentration in the plasma was achieved within 24–48 h after oral/rectal administration of nimesulide (100 mg twice daily). In another study, Gandini et al (1991) observed that the hydroxy metabolite reached its highest plasma concentration (3·03 μg mL^{-1}) at 5·33 h, with an apparent half-life of 4·78 h, following oral administration of nimesulide (200 mg). Recently, Sarkar et al (1997) have reported the presence of an unknown compound known as "the purple spot" in race-track urine samples. This compound was not positively identified until nimesulide was found in the blood samples and it was postulated to be a urinary metabolite of nimesulide formed by the reduction of the nitro group on nimesulide to an amino group (4-amino-2-phenoxy-methanesulphonanilide).

Recently, Carini et al (1998) characterized and quantitatively determined the main urinary metabolites of nimesulide in man following a single oral administration of 200 mg. These were found to arise from hydroxylation of the phenoxy nucleus (M1), reduction of the nitro group to an amino derivative (M2), concomitant hydroxylation and reduction (M3), and *N*-acetylation of the M2 (M4) and M3 (M5) metabolites (Figure 2). The bulk of the metabolites were in conjugated form and accounted for approximately 40% of the administered dose. The percentage excretion of the unchanged drug and the metabolite M4 were below 0·5%. The lower recovery in the urine was attributed to incomplete gastrointestinal absorption and to consistent faecal excretion of the metabolites.

Table 4 summarises the pharmacokinetic parameters of nimesulide after the administration of a single dose to human volunteers, as determined by various researchers.

Dose

A parallel-group study (comprising 392 patients) was undertaken for one month to define the optimal dose of nimesulide for the treatment of painful osteoarthritis (Bourgeois et al 1994). The mean values of pain intensity for nimesulide groups (50, 100 or 200 mg twice daily) were similar and significantly lower than the mean for the placebo group. The patients' and the physicians' overall judgement of the drug's efficacy demonstrated significant differences between nimesulide 100 and 200 mg, with a greater (although not significantly so) incidence of adverse events (23 vs 13%) with the higher dose. Thus, nimesulide 100 mg twice daily was considered to be the optimal dose for the treatment of osteoarthritis.

Nimesulide Versus Other NSAIDs

The relative efficacy of nimesulide versus other NSAIDs is given in Table 5, whereas Table 6 summarises a qualitative comparison of non-selective and selective COX-2 inhibitors (Mandell 1999).

Drug Interactions

NSAIDs are prescribed for long-term use in a variety of pathological conditions. As a result, they are frequently prescribed in combination with other medications, indicating a considerable propensity for interactions. Potential drug interaction studies between nimesulide and a variety of other drugs have been carried out in a limited number of investigations. Most of the interactions that have been reported to date are unlikely to be of any clinical importance. Nimesulide differs from conventional NSAIDs in its structure and pharmacological profile. The interaction potential of nimesulide might also differ from that of other NSAIDs (Perucca 1993).

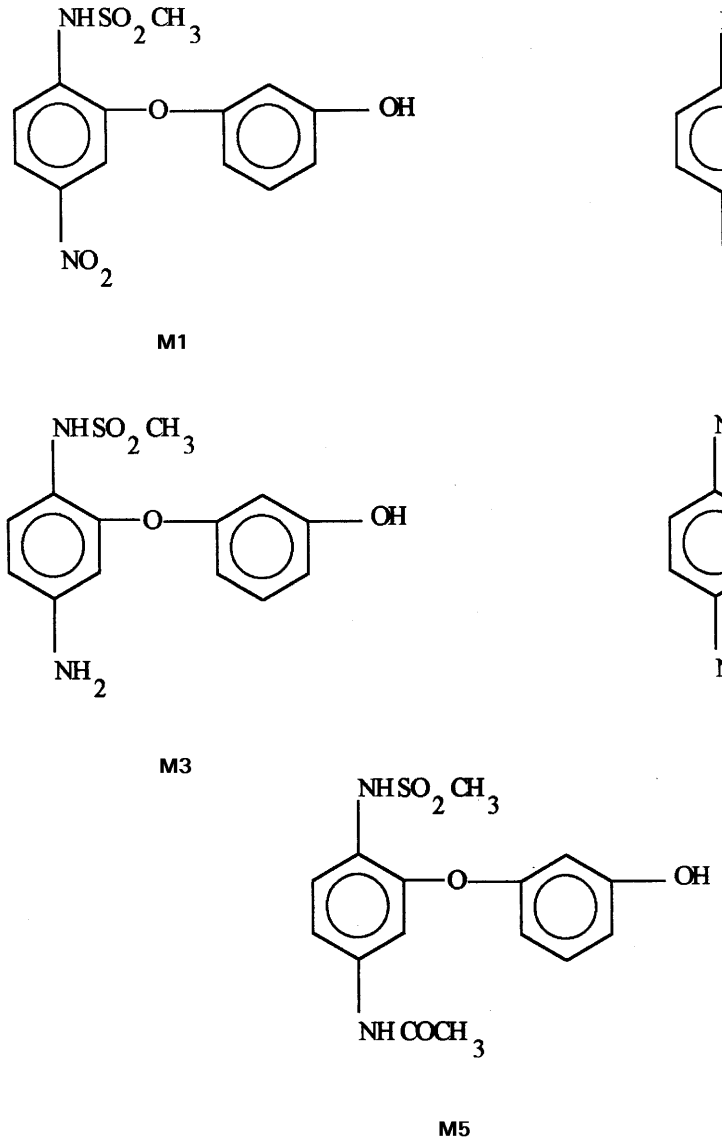

Figure 2. Urinary metabolites of nimesulide in man (Carini et al 1998).

Table 4. Summary of pharmacokinetic studies on nimesulide in volunteers.

Dosage form	Dose (mg)	No. of subjects	C_{max} ($mg\,L^{-1}$)	T_{max} (h)	$T_{1/2\beta}$ (h)	Cl/F ($mL\,h^{-1}\,kg^{-1}$)	AUC ($mg\,L^{-1}\,h^{-1}$)	Reference
Tablets	100	6m[a]	2·62	3·33	3·74	–	21·09	Pandya et al (1997)
Tablets	100	6m[a]	2·66	3·17	3·30	–	22·36	
Granules	50	14[b]	3·46	1·93	2·40	–	18·40	Ugazio et al (1993)
Tablets	100	18 (fasted)	3·83	1·86	2·00	82·34	17·67	Lucker (1992)[c]
Tablets	100	18 (fed)	3·02	1·75	2·21	90·88	15·89	
Granules	100	18 (fasted)	4·11	1·34	2·27	81·30	18·30	
Suspension	100	18	4·58	1·22	2·00	81·81	18·37	Lucker (1991)[c]
Suspension	100	18	4·18	1·89	2·06	86·18	17·50	
Granules	100	18	4·26	1·78	1·96	86·41	17·32	
Oral	200	6m	8·09	3·50	5·27	35·64	97·15	Gandini et al (1991)
Oral	200	6f	11·61	2·83	4·64	65·87	66·80	
Suppository	200	3m + 3f	2·71	12·00	8·62	95·90	52·70	Bernasconi (1989)[c]
Suppository	200	12 (6m + 6f)	2·32	4·17	5·75	131·00	27·30	DeCaro (1989)[c]

[a]Two different commercial formulations; [b]Hypoglycaemic children; m, males; f, females;[c]data on file, Helsinn Healthcare.

Table 5. Summary of comparative trials of nimesulide versus other NSAIDs.

Route of administration	Treatment	Relative efficacy	Reference
Topical	Nimesulide 10 mg Piroxicam 10 mg Diclofenac 10 mg	Nimesulide > Diclofenac > Piroxicam	Sengupta et al (1998)
Oral	Nimesulide 100 mg bd Diclofenac 75 mg bd	Nimesulide > Diclofenac	Wober et al (1998)
Oral	Nimesulide 200 mg/day Methoxybutropate 1200 mg/day	Nimesulide ≅ Methoxybutropate	Melis et al (1997)
Oral	Floctafenine 200 mg Nimesulide 100 mg Paracetamol 500 mg	Floctafenine was a valid alternative for many patients who reacted adversely to other NSAIDs	Giuseppe et al (1997)
Oral	Nimesulide 200 mg/day Etodolac 600 mg/day	Physician's assessment significantly in favour of nimesulide but patients showed no bias. Etodolac was better tolerated.	Lucker et al (1994)
Oral	Nimesulide 100 mg bd Naproxen sodium 550 mg bd	Higher incidence of side effects with naproxen sodium but without any statistical difference, no statistical difference between the two treated groups regarding general clinical examination and biological follow up.	Lecomte et al (1994)
Rectal	Nimesulide 200 mg Paracetamol 500 mg tid for 2 days	Nimesulide as active and safe as paracetamol in treating hyperpyrexia in the aged	Cunietti et al (1993)
Oral	Nimesulide 100 mg bd for 7 days Seaprose-S 100 mg bd for 7 days	Efficacy of seaprose-S > nimesulide. Greater safety of seaprose-S.*	Antonelli et al (1993)
Oral	Nimesulide 50 mg bd for 5 days Lysine aspirin 360 mg bd for 5 days	Nimesulide and lysine aspirin equally effective in the treatment of inflammation of respiratory tract but nimesulide was better tolerated by the gastrointestinal tract	Barberi et al (1993)
Rectal	Nimesulide 200 mg bd Ketoprofen 250 mg bd	Nimesulide demonstrated greater efficacy and a more rapid anti-inflammatory effect than ketoprofen	Pierleoni et al (1993)
Oral	Nimesulide 100 mg bd Naproxen 250 mg bd	Nimesulide > Naproxen**	Parabita et al (1993)
Rectal	Nimesulide 200 mg bd for 5 days Ketoprofen 100 mg bd for 5 days	Nimesulide > Ketoprofen as evaluated by the physicians† and patients††	Coscarelli et al (1993)
Oral	Nimesulide 100 mg/12 h Fentiazac 100 mg/12 h Mefenamic acid 500 mg/8 h	Nimesulide was useful in pain associated with dysmenorrhoea with a little statistical advantage over fentiazac but bigger statistical advantage over mefenamic acid	Rosales et al (1989)

*$P < 0{\cdot}01$. **$P = 0{\cdot}008$. †$P = 0{\cdot}0001$. ††$P = 0{\cdot}023$.

Taniguchi et al (1996) demonstrated that the administration of nimesulide alone induced clonic convulsions at a dose greater than 300 mg kg^{-1} and that enoxicam induced no convulsions even at a dose above 5000 mg kg^{-1}, in mice. However, a combination of nimesulide (200 mg kg^{-1}) and enoxicam (400 mg kg^{-1}) induced no convulsions. This suggested their possible use in combination to reduce convulsions in clinical settings.

Auteri et al (1991a) demonstrated that no statistically significant changes were observed in prothrombin time, partial thromboplastin time, fibrinogenaemia or the bleeding time in patients already taking warfarin (5 mg daily) and undergoing simultaneous treatment with nimesulide (100 mg twice daily 7 days). The interaction between nimesulide (100 mg twice daily) and slow-release theophylline (200 mg twice daily) was also investigated by Auteri et al (1991b), who observed no pharmacodynamic interaction between them. However, addition of nimesulide resulted in a statistically significant ($P < 0{\cdot}01$) decrease in mean

Table 6. Qualitative comparison of nonselective and COX-2 selective NSAIDs (Mandell 1999).

	Non selective NSAIDs	COX-2 selective NSAIDs
Incidence of side effects		
Gastric ulcers, bleeding, perforation, obstruction	Uncommon*	Close to placebo†
Decreased platelet function	Common	None
Decreased renal function (reversible) in patients at risk	Uncommon	Unknown
Bronchospasm (in sensitive patients)	Uncommon	Unknown
CNS side effects	Rare*	Unknown
Efficacy in treating		
Acute pain	Moderate*	Unknown
Pain in chronic osteoarthritis	Moderate	Moderate
Pain in rheumatoid arthritis	Moderate	Moderate
Pain in acute migraine	Moderate*	Unknown
Pain in chronic spondylitis	Mild*	Unknown
Pain in acute gout	Strong*	Unknown
Approved for children	Yes*	No

*Differs among individual NSAIDs; †longer follow-up of patients using these drugs is required.

theophylline AUC values (from $133{\cdot}1 \pm 29{\cdot}0$ to $118{\cdot}5 \pm 29{\cdot}9\,\mathrm{mg\,L^{-1}\,h^{-1}}$) but pharmacokinetics of nimesulide and 4-hydroxy nimesulide were not altered. A slight decrease in theophylline concentration was neither clinically nor biologically significant but was thought to be due to enzyme induction. However, no significant drug interactions have been observed between nimesulide and glibenclamide, cimetidine, antacids, furosemide or digoxin (Bernareggi 1998).

Tolerability of Nimesulide

NSAIDs have been implicated in a number of adverse effects. The mechanism provoking these have not been fully elucidated, but could be due to COX inhibition. Nimesulide, because of its selectivity for COX-2 and a display of additional properties in terms of its effects on inflammation mediator synthesis and release, enables it to be generally well tolerated by NSAID-intolerant patients and in patients with NSAID-induced asthma. Several studies in NSAID-intolerant patients with asthma demonstrated that therapeutic doses of nimesulide did not induce asthmatic attacks, while higher doses (400 mg) precipitated mild asthma in only 10% of patients (Senna et al 1996).

In a study by Pastorello et al (1998), test doses of nimesulide and paracetamol were administered to 367 patients of which 208 had a history of reactions only to NSAIDs and 148 to NSAIDs and antimicrobials. It was observed that atopy and history of allergic reactions to the antimicrobial drug increased the likelihood of intolerance of paracetamol and nimesulide in subjects allergic to NSAIDs. Quaratino et al (1997) investigated the long-term tolerability of nimesulide and paracetamol in NSAID-intolerant patients ($n = 248$) who had tolerated oral challenges with nimesulide, paracetamol, or both, 1–3 years earlier. Nimesulide was tolerated by 94·2% patients and paracetamol by 94·6%. A total of 5% of patients had experienced reactions (7 urticarial and 1 asthmatic) to one or both of the drugs. Intolerance was unrelated to the nature of the condition treated or to the number of doses administered but the patients who failed to tolerate paracetamol and those who reacted to nimesulide had previous histories of chronic urticaria.

The tolerability of nimesulide in patients with clear histories of NSAID intolerance was assessed in 429 patients (Andri et al 1994). A single-blind challenge was carried out with cumulative doses of nimesulide administration on three different days, until the therapeutic dose (200 mg) was reached or symptoms of intolerance developed. Nimesulide was well tolerated by 418 patients and thus it seemed to be a suitable drug in cases of aspirin hypersensitivity. Oral treatment with nimesulide (200 mg daily for 15 days) or placebo was administered to 40 female patients (aged 14–65 years) affected by mastodynia associated with benign breast disease (Dionigi et al 1992). The administration of nimesulide was associated with a clinically significant attenuation of mammary tenseness and mastodynia in the majority of cases. No adverse reaction was observed as a result of nimesulide therapy. In a study by Asero (1998), tolerance to paracetamol or aspirin was investigated in 9 patients with a history of nimesulide-induced urticaria. Paracetamol was well tolerated by all 9 patients but 2 patients experienced

immediate systemic urticaria after the administration of aspirin (125 mg). It was concluded that though paracetamol and aspirin were well tolerated by most nimesulide-sensitive patients, tolerance should always be ascertained by per-oral challenge.

Nimesulide (100 mg granules twice daily) or a combination of aspirin and vitamin C (500 mg + 300 mg) was administered to 39 outpatients suffering from seasonal epidemic influenza (Bernasconi & Massera 1985). A rapid and complete recovery was achieved in all patients. However, nimesulide was better tolerated with only one patient complaining of gastralgia, against six cases of side effects reported with aspirin + vitamin C.

A post-marketing survey (Pochobradsky et al 1991) was carried out to assess the therapeutic efficacy and tolerability of nimesulide in 22 938 patients suffering from osteoarthritis. Nimesulide was administered as tablets (40% patients) or granules (60% patients) at a dose varying between 100 and 400 mg daily for a period of 1–3 weeks. Eight percent of patients reported adverse gastrointestinal effects. A review (Fusetti et al 1993) described the tolerability of nimesulide as documented in a global assessment of the clinical data available to Helsinn for this drug. Data from 151 trials were considered. Of 4945 subjects treated with nimesulide (100 mg twice daily; orally to 90% patients and rectally to 10%), 349 (7·1%) experienced adverse effects and 52 (1·1%) withdrew from the treatment. Analysis of the adverse events by body system showed the highest incidence associated with the digestive system (72·1%) followed by the body as a whole (11·7%), skin (6·9%) and the nervous system (6·0%). The events attributed to the digestive system were principally diarrhoea, gastric irritation, gastritis, heartburn, nausea and vomiting. The treatment was also associated with a small number (n = 5) of adverse events related to metabolic (n = 2), urinary (n = 1) and respiratory (n = 2) systems. There was no evidence that dosage formulation or the route of administration affected the incidence or the nature of the adverse effects. However, a male patient, aged 29 years, with HIV infection reported thrombocytopenia on two different occasions (2 months apart) after the administration of nimesulide (Pasticci et al 1990). The symptoms resolved after withdrawing the drug.

Clinical Opportunities

In addition to anti-inflammatory, analgesic and antipyretic activity in the treatment of a variety of conditions (Table 7), clinical experience with nimesulide has demonstrated that patients receiving a combination of nimesulide (200 mg daily) and terfenadine (120 mg daily) showed significantly better improvements as compared with those who received either terfenadine or placebo (Andri et al 1992). This suggests the possible use of a combination of nimesulide with antihistamines.

Colon cancer

The observation that COX-2 is highly expressed in human and animal colon cancer cells as well as in colorectal adenocarcinomas (Gustafson-Svard et al 1996) has led to the belief that COX activity is involved in the process leading to colon cancer. This is further supported by studies in the mutant *Apc* mouse, which is a model of familial adenomatous polyposis in man. The spontaneous development of intestinal polyposis in these mice was strongly reduced either by the deletion of the COX-2 gene or by treatment with a selective COX-2 inhibitor (Eberhart et al 1994; Oshima et al 1996). In another study (Nakatsugi et al 1997) it was observed that nimesulide reduced the number of both small and large intestinal polyps by 52% in *min* mice, when compared with vehicle-treated *min* mice. Nimesulide was also found to suppress the formation of aberrant crypt foci induced by azoxy methane within rat colons (Takahashi et al 1996). Similar results have been reported for other selective COX-2 inhibitors (Reddy et al 1996; Kawamori et al 1998). Thus, it is highly likely that selective COX-2 inhibitors could be used prophylactically to prevent colon cancer in genetically

Table 7. Clinical uses of nimesulide (Tognella 1993).

Analgesia	Oncology
	Dental surgery
	Post operative pain
	Menstrual headache
Dentistry	Stomatitis
	Gingivitis
	Periodontitis
	Periapical abcess
ENT	Rhinitis
	Pharyngitis
	Tonsillitis
	Otitis
Gynaecology	Mastodynia
	Pelvic inflammatory disease
	Dysmenorrhoea
Musculoskeletal system and connective tissue	Osteoarthritis
	Bursitis
	Tendinitis and tenosynovitis
	Low back pain
Ophthalmology	Inflammation of the eye
	Adnexa
Respiratory conditions	Acute and chronic bronchitis
Sports related injury	Coadjuvant in traumatism
Urology	Prostatitis
	Urethritis

susceptible individuals, without causing gastrointestinal damage themselves (Vane & Botting 1998).

Alzheimer's disease

The suggested role of COX in Alzheimer's disease is based on epidemiological findings (Breitner 1996). Stewart et al (1997) observed that ibuprofen reduced the severity of Alzheimer's disease, whereas no such effect was seen with paracetamol. The protective effect of NSAIDs is consistent with evidence of anti-inflammatory activity in the pathophysiology of Alzheimer's disease (Hampel & Muller 1995; Yan et al 1997). Surprisingly, it was observed that the total COX-2 content of brain tissue from patients with Alzheimer's disease was lower than normal (Chang et al 1996). It was argued that COX-2 levels could have been on the higher side during the early stages of the disease, but that large loss of neuronal tissues in the later stages of the disease might have resulted in decreased levels. In fact, Pasinetti & Alsen (1998) observed an upregulation of COX-2 expression in the frontal cortex in Alzheimer's disease. Further, it was observed that synthetic β-amyloid peptides induced COX-2 expression in SHSY5Y neuroblastoma cells in-vitro, suggesting a mechanism for COX-2 upregulation in Alzheimer's disease.

Selective COX-2 inhibitors may, therefore, slow the progress of Alzheimer's disease without any damaging effect on the stomach mucosa (Stewart et al 1997). Thus, COX-2 inhibitors could have a major benefit in the early treatment of individuals who are asymptomatic but genetically at risk. However, further studies in a specific Alzheimer's disease model are needed before drawing any conclusion.

Analytical Procedures

Determination of nimesulide and its metabolite in plasma

Very few analytical procedures have been reported for the estimation of nimesulide in dosage forms and in biological samples. One of the first techniques for the quantitative analysis of nimesulide in plasma by high-speed liquid chromatography was reported by Chang et al (1977). This was a sensitive and chemically specific method with a low sensitivity limit of $0{\cdot}2\,\mu g\,mL^{-1}$ and was successfully applied to the plasma-level determination of the drug in man and rats in metabolic experiments at pharmacological doses. Castoldi et al (1988) developed a direct assay for simultaneously determining plasma and urine levels of nimesulide and 4-hydroxy nimesulide. This HPLC method permitted an excellent separation of nimesulide and 4-hydroxy nimesulide with a sensitivity of $50\,ng\,mL^{-1}$ for both the drug and its metabolite. An HPTLC method developed by Pandya et al (1997) constituted a sensitive and specific assay for nimesulide in human plasma after the administration of therapeutic doses. This technique was economical, faster and utilized less solvent. Unlike other methods, an internal standard was not required and the quantification could be performed with the aid of an external standard. More recently, Carini et al (1998) undertook a study to characterize and quantitatively determine the main urinary metabolites of nimesulide in man following single oral administration (200 mg). The quantification was performed by reverse-phase HPLC which permitted the simultaneous determination of the unchanged drug and its metabolites in a single chromatographic run. Another HPLC method for the estimation of nimesulide and 4-hydroxy nimesulide (limit of quantification $25\,ng\,mL^{-1}$ for nimesulide and 4-hydroxy nimesulide) in human plasma has been reported by Giachetti & Tenconi (1998).

Determination of nimesulide in dosage forms

Besides the high-precision techniques mentioned above, various assay procedures for the estimation of nimesulide in dosage forms have been reported. These include a number of spectrophotometric (Fallavena & Schapovral 1995; Chowdary et al 1997, 1999; Reddy et al 1998) and fluorimetric (Lakshmi et al 1998) methods.

Conclusions

Nimesulide is a unique NSAID with a very high affinity for selective inhibition of COX-2. Due to this selectivity, it exhibits a high degree of anti-inflammatory, antipyretic and analgesic activity. The mode of action of this drug is mediated not only through prostaglandin inhibition, but also through its effects on neutrophil functions including respiratory burst, integrin-mediated adherence and synthesis of PAF. Various researchers have also reported free-radical scavenging activity, which could prevent free-radical mediated tissue damage in inflammatory conditions. Others have reported its inhibitory effects on histamine release from basophils. Recent studies have provided evidence that a more complex relationship may exist in inflammatory conditions, as COX-2 mRNA was found in the brain, kidneys and stomach of mice

and rats, suggesting that COX-2 might play an important role in housekeeping.

The anti-inflammatory activity of nimesulide has been demonstrated in patients with a large variety of inflammatory conditions. In double-blind trials nimesulide has been at least as effective as currently available NSAIDs, though with less side effects and a better tolerability profile.

Apart from their anti-inflammatory activity, selective COX-2 inhibitors have the potential to replace NSAIDs for the relief of arthritic symptoms. They may also find use in Alzheimer's disease, colon cancer, in the prevention of preterm labour and in intestinal epithelium after bacterial infections. When compared with toxicity of currently available NSAIDs, specific COX-2 inhibitors are likely to provide safer therapeutic alternatives, while hopefully being as efficacious as current agents, if not more so. Their degree of success will depend a lot on their long-term safety profile.

Pharmaceutically, nimesulide has not been explored extensively, with only a few published papers. Due to its poor aqueous solubility, problems could arise in its formulation. This has been successfully overcome by complexation of the drug with β-cyclodextrin. However, lack of in-vivo data for such complexes may clinically limit their use and be of little significance.

On the analytical front, only a few published reports have appeared for the quantitative estimation of the drug and its metabolites in human plasma and urine.

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