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Are there any Differences among Non-Steroidal Anti-Inflammatory Drugs? Focus on Nimesulide

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Abstract

Although the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) as anti-inflammatory, analgesic and antipyretic agents is well established, there is still an open question as to whether their different pharmacokinetic and pharmacodynamic characteristics do have a different clinical impact in treating rheumatology patients.

The mechanism related to the anti-inflammatory activity of these drugs is mainly related to the inhibition of the cyclo-oxygenase (COX)-2 isoform, whereas inhibition of COX-1 is associated with the side effects of these drugs. However, some NSAIDs exert their anti-inflammatory and analgesic action by additional mechanisms.

The NSAID nimesulide, along with its preferential activity on COX-2 and a short half-life that correlates with a rapid onset of analgesic action, acts also through a variety of COX-independent pathways that contributes to its potent anti-inflammatory and analgesic activity.

The pathways affected by nimesulide include inhibition of tumour necrosis factor alpha (TNF-α) release, histamine release, reactive oxygen species production and chondrocyte death. Furthermore, the use of nimesulide has been associated with reduced levels of matrix metalloproteases and other biomarkers of joint destruction, suggesting it may have a protective effect against disease progression.

Due to its multifactorial mechanism as well as to rapid onset of the analgesic action, nimesulide represents an appealing therapeutic choice for the treatment of rheumatology patients.

Introduction

The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) is well established. As a group, NSAIDs share anti-inflammatory, analgesic and antipyretic activities. However, these agents belong to different chemical classes and may have different pharmacokinetic and, to some extent, pharmacodynamic characteristics. This raises questions as to whether any clinically significant differences exist between NSAIDs, and whether potential differences should be considered when deciding which NSAID to use to relieve pain and inflammation in rheumatology patients.

According to a comprehensive systematic review of the clinical efficacy of NSAIDs, different

agents appear to have similar therapeutic activities.[1] However, other data suggest that differences in the pharmacological profiles of NSAIDs may have implications for the efficacy of these compounds in rheumatology patients. This paper will explore some of these differences, focusing particularly on the NSAID nimesulide.

Pharmacological Properties of Non-Steroidal Anti-Inflammatory Drugs

Inhibition of prostaglandin synthesis

In the early 1970s, Vane[2] noticed that aspirin and similar drugs were able to inhibit the biosynthesis of a group of lipid mediators, known as prostaglandins, by inhibiting an enzyme responsible for their production named cyclo-oxygenase (COX). This inhibitory activity seemed to be at the basis of the anti-inflammatory activity of these drugs. Only 20 years later, it became evident that two isoforms of the COX enzyme, COX-1 and COX-2, were responsible for prostaglandin production, and that NSAIDs differ in their selectivity for the different COX isoforms.[3] COX-1 is mainly responsible for the production of prostaglandins involved in homeostasis in key organs, such as the stomach, and COX-1 inhibition may account for the well-known gastrointestinal side effects of traditional NSAIDs. COX-2 mediates the synthesis of inflammatory prostaglandins, and the inhibition of this isoform is thought to produce the therapeutic anti-inflammatory effects of a NSAID.[4–6] Non-selective NSAIDs inhibit both COX-1 and COX-2 by binding reversibly or irreversibly to the enzyme. The major toxicities associated with these agents are thought to result from their ability to block the synthesis of physiological prostaglandins required for homeostasis in the kidney, stomach, and platelets via COX-1 inhibition.

The mechanisms of NSAID-associated toxicity have been further investigated, and it is evident that a number of different factors may influence the safety of these agents. The introduction, in the late 1990s, of the selective COX-2 inhibitors (coxibs) was based on an expectation that these agents would confer clinical efficacy with reduced gastrointestinal toxicity.[4–6] However, recent evidence that selective COX-2 inhibitors are associated with an increase in thrombotic events[7–11] led to the worldwide withdrawal of rofecoxib and valdecoxib, this last due to alert related to skin reactions as well.[7–9] These findings may be supported by evidence that blocking COX-2-derived prostacyclin removes a protective effect on thrombogenesis, hypertension and atherogenesis *in vivo*,[4] although debate on this issue is ongoing. Therefore, the expected benefits of the selective COX-2 inhibitors might be negated by their potential for increased cardiovascular toxicity compared with other NSAIDs.[4–6]

The degree of COX isoform selectivity remains one of the main ways of differentiating among NSAIDs (see figure 1).[3,12] COX selectivity is a consequence of the chemical structure of the NSAID.[13] The amino acid structures of COX-1 and COX-2 are highly conserved, but X-ray crystallographic studies of COX show that the channel containing the active NSAID binding site on COX-2 allows the acceptance of a wider range of substrates than that of COX-1. This active channel is hydrophobic, and, in COX-2, a valine substitution for isoleucine on amino-acid position 523 allows for an open hydrophilic side pocket, which is closed by isoleucine in COX-1. For example, the non-selective NSAID flurbiprofen interacts with COX-1 through phenyl binding to the hydrophobic channel and carboxylic group binding to arginine at position 120. The interaction of flurbiprofen is similar with COX-2, but the carboxylic group binding to arginine 120 blocks substrate from the COX-2 active site. Conversely, selective COX-2 inhibitors are unable to enter the active channel of COX-1, and do not have a carboxylic group to bind to arginine 120.

In the NSAIDs setting nimesulide appears to be a rather unique molecule, being the only representative of the sulphonanilides class.

With reference to the degree of selectivity towards COX isoforms, nimesulide could be defined

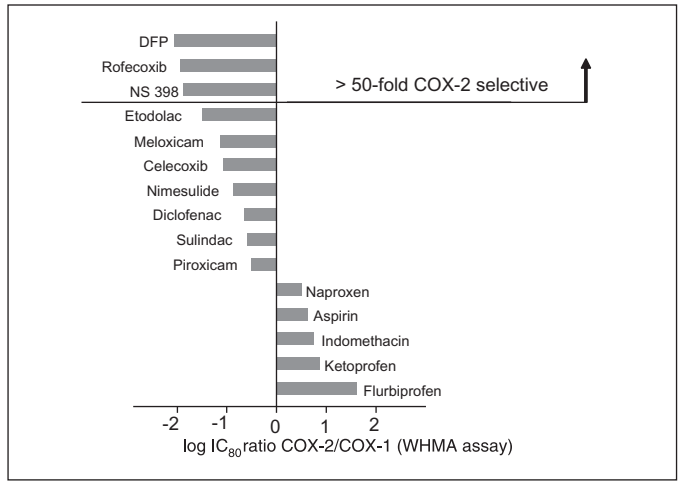

Fig. 1. Non-steroidal anti-inflammatory drugs selectivity for cyclo-oxygenase-1 and -2. **COX** = cyclo-oxygenase; **DFP** = diisopropyl; **WHMA** = William Harvey Human Modified Whole Blood Assay. Reproduced from Warner et al.,[3] with permission.

as a preferential COX-2 inhibitor, showing a 5- to 50-fold selectivity for COX-2 over COX-1.[3] In *in vivo* studies, nimesulide, at therapeutic doses (100 mg twice a day) was shown to decrease plasma prostaglandin E_2 concentration significantly. An evaluation of the indices of COX-1 activity showed nimesulide to have no effect on platelet aggregation. Also the drug has no effect on the gastric production of prostaglandin E_2 and on prostaglandin I_2, known also to be COX-1 dependent.[14]

Pharmacokinetic Profile

Pharmacokinetic parameters differ considerably among different NSAIDs. On the basis of their half-lives, NSAIDs can generally be divided into two groups: those with a short half-life (< 6 h) and those with a long half-life (> 10 h).[15] NSAIDs with a short half-life include aspirin, diclofenac, ibuprofen, flurbiprofen, indomethacin, lumiracoxib and nimesulide,[15–19] whereas those with a long half-life include celecoxib, naproxen, sulindac, rofecoxib, oxaprozin and piroxicam.[15–19] Because steady-state plasma concentrations are attained after a period of administration extending over three to five half-lives, NSAIDs with short half-lives achieve peak plasma concentrations and maximum clinical benefits more rapidly than those with long half-lives.[15,20]

Nimesulide: Pharmacological Profile

In patients with acutely inflamed arthritic joints, nimesulide had a rapid onset of action, with early inhibition of the production of prostaglandin E_2 taken as a marker of COX-2 activity.[21] Clinical evidence of the fast onset of action of nimesulide came from a study in patients with osteoarthritis of the knee, in which nimesulide provided significantly more rapid relief from pain associated with walking than celecoxib and rofecoxib; the onset of analgesic action was evident 15 min after nimesulide intake.[22] In addition, recent data show that effective concentrations of nimesulide can be detected both in plasma and synovial fluid 30 min after drug intake.[23] These characteristics conceivably account for the rapid analgesic action of this NSAID.

NSAIDs may also exert COX-independent anti-inflammatory effects.[20] In addition to the preferential COX-2 inhibitory activity that contributes to the anti-inflammatory and analgesic properties of nimesulide, this agent has been shown to act via several COX-independent pathways.[24]

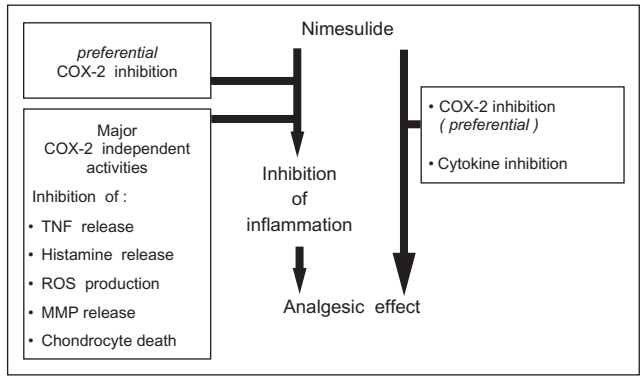

Fig. 2. Multifactorial mode of action of nimesulide. **COX** = cyclo-oxygenase; **MMP** = metalloprotease; **ROS** = reactive oxygen species; **TNF** = tumour necrosis factor.

The pathways affected by nimesulide include inhibition of tumour necrosis factor (TNF) release, histamine release, reactive oxygen species (ROS) production, matrix metalloprotease (MMP) release, and chondrocyte death (see figure 2).

Effects of Nimesulide on Inflammatory Mediators

In the temporal and functional hierarchy of biological events of the inflammation process, TNF-α is considered to play a pivotal role, making it an ideal therapeutic target in rheumatoid arthritis. In a preclinical study with rats injected with lipopolysaccharide to increase levels of TNF-α, nimesulide inhibited the release of TNF-α efficiently.[25]

The production of superoxide by phagocytes and the release of lactoferrin by neutrophils were measured in eight volunteers before and after the oral administration of nimesulide.[26] The chemotactic factor *N*-formyl-methionyl-leucyl-phenylalanine and opsonized zymosan particles were used as activating stimuli. Nimesulide significantly inhibited ROS production by *N*-formyl-methionyl-leucyl-phenylalanine and opsonized zymosan particle-triggered phagocytes (67.6% and 36.8% inhibition, respectively; see figure 3).[26] Lactoferrin release by neutrophils was not affected, suggesting that nimesulide does not interfere with mechanisms involved in the exocytosis of specific granules.

The prevention of tissue damage during inflammatory reactions requires the maintenance of a balance between proteinases (mainly elastases released by locally recruited neutrophils) and antiproteases (mainly the elastase-specific alpha-1-proteinase inhibitor; A1PI).[27] Neutrophil cells

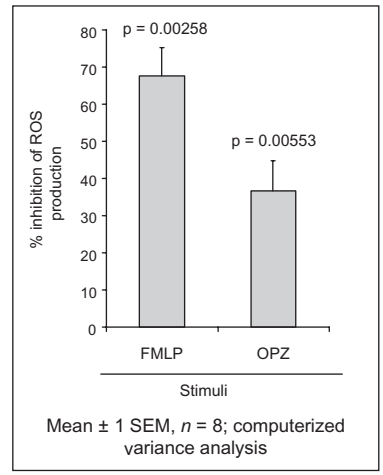

Fig. 3. Effect of nimesulide on reactive oxygen species production by phagocytes in normal volunteers. **FMLP** = *N*-formyl-methionyl-leucyl-phenylalanine; **OPZ** = opsonized zymosan particles; **ROS** = reactive oxygen species; **SEM** = standard error of the mean. Adapted from Ottonello et al.,[26] with permission.

are able to inactivate A1PI via several oxidants, including hypochlorous acid, leaving elastase free to break down connective tissue. A possible approach to regulate neutrophil elastase activity is to rescue A1PI pharmacologically from oxidative inactivation by hypochlorous acid from neutrophils. In a preclinical study,[27] nimesulide prevented the inactivation of A1PI by hypochlorous acid released by neutrophils, thereby permitting the A1PI-mediated control of histotoxic elastase function. These data suggest that the protective effect of nimesulide on A1PI may contribute to its anti-inflammatory effects.

In another study,[28] histamine release and bronchoconstriction were inhibited in a dose-dependent manner in guinea pigs treated with nimesulide (see figure 4). Guinea pigs were pretreated with nimesulide or indomethacin; then histamine release and bronchoconstriction were induced with acetaldehyde. Blood concentrations of histamine were 195 ± 12 μg/l in guinea pigs treated with acetaldehyde alone (controls), 154 ± 10 μg/l in nimesulide 0.1 mg/kg recipients, ($p < 0.05$ versus controls), 116 ± 13 μg/l in nimesulide 0.3 mg/kg recipients ($p < 0.01$ versus controls), 63 ± 8 μg/l in nimesulide 1 mg/kg recipients ($p < 0.01$ versus controls) and 222 ± 16 μg/l in indomethacin 1 mg/kg recipients. This dose-dependent decrease by nimesulide in circulating concentrations of histamine was paralleled by dose-dependent protection against the bronchoconstrictive effect of acetaldehyde. Mean bronchoconstriction (as measured by intratracheal pressure expressed as a percentage of maximal overflow) was 58% in control guinea pigs, 42% in nimesulide 0.1 mg/kg recipients ($p < 0.05$ versus controls), 28% in nimesulide 0.3 mg/kg recipients ($p < 0.01$ versus controls), 15% in nimesulide 1 mg/kg recipients ($p < 0.01$ versus controls) and 62% in indomethacin 1 mg/kg recipients. Whereas indomethacin did not reduce histamine levels or protect against bronchoconstriction, nimesulide had a dose-dependent bronchoprotective effect and reduced histamine blood levels. These observations might be of therapeutic relevance in patients with inflammation of the respiratory tract and a history of allergic bronchoconstriction.[28]

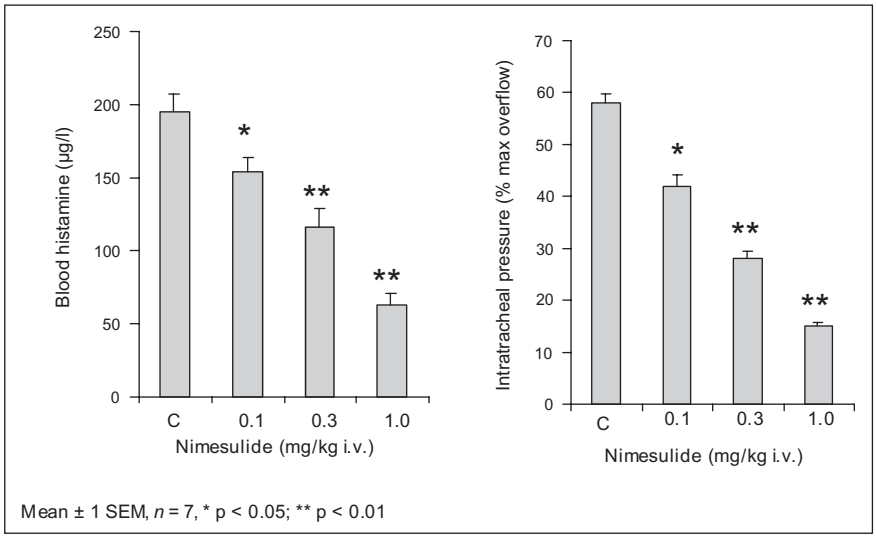

Fig. 4. Effect of nimesulide on the release of histamine and bronchoconstriction in guinea pigs. **SEM** = standard error of the mean. Adapted from Rossoni et al.,[28] with permission.

Effects of Nimesulide on Bone and Cartilage

In osteoarthritis, MMP-1, MMP-8 and MMP-13 play pivotal roles in the degradation of type II collagen, whose fragments are further broken down by MMP-3.[29,30] In patients with osteoarthritis, serum levels of MMP were reduced with nimesulide.[31] In this open-label pilot study, 20 patients with osteoarthritis of the knee or hip and acute pain received nimesulide 100 mg twice a day for 3 weeks and 22 healthy control subjects received no treatment. In addition to an improvement in pain compared with no treatment, nimesulide therapy significantly reduced mean serum levels of MMP-3 (from 21.1 ng/ml at baseline to 14.7 ng/ml; $p < 0.01$) and MMP-8 (from 14.5 ng/ml to 10.0 ng/ml; $p < 0.05$). Therefore, nimesulide may inhibit extracellular matrix digestion by reducing levels of MMP-8 and MMP-3.

In addition, nimesulide was more effective than ibuprofen in obtaining a reduction in urinary levels of collagen type II C-telopeptide (CTX-II) and serum levels of hyaluronan (HA), MMP-3 and MMP-13 in patients with a flare-up of osteoarthritis.[32] Hyaluronan is a marker of synovium inflammation, and CTX-II is a marker of cartilage collagen degradation; both substances are known to be prognostic for a poor outcome in osteoarthritis. In that randomized, prospective, single-blind study, 90 patients received nimesulide 100 mg twice a day ($n = 45$) or slow-release ibuprofen 800 mg twice a day ($n = 45$) for 4 weeks. At the end of the treatment, mean serum levels of hyaluronan decreased significantly in the nimesulide group (from 59 to 42 ng/ml; $p < 0.05$) but not in the ibuprofen group (from 62 to 52 ng/ml). Similarly, mean urinary levels of CTX-II decreased significantly with nimesulide (from 0.42 to 0.31 μg/mmol creatinine; $p < 0.001$), but not with ibuprofen (from 0.42 to 0.38 μg/mmol creatinine). Nimesulide also significantly reduced mean serum levels of both MMP-3 (from 37 to 27 ng/ml; $p < 0.05$) and MMP-13 (from 92 to 58 pg/ml; $p < 0.001$), whereas no such significant effect was noted with ibuprofen treatment. In addition, the decrease in CTX-II levels in nimesulide recipients correlated strongly with the reduction in hyaluronan and MMP-13.

It is of note that nimesulide may also have a protective effect in osteoarthritis by shielding chondrocytes (the cells responsible for cartilage regeneration) from apoptosis.[33] To evaluate the effect of different NSAIDs on chondrocytes, a chondrocyte cell line was exposed to staurosporine to induce apoptosis. Cultures were carried out with nimesulide, ibuprofen or the selective COX-2 inhibitor NS 398. At 4 h, staurosporine-induced apoptosis was significantly reduced in chondrocytes pretreated with nimesulide (see figure 5) or ibuprofen in a concentration-dependent manner (10^{-12} to 10^{-6} mol/l). However, NS 398 did not provide such protection. Cell death seemed to be occurring via changes in BCL-2 gene expression and caspase-3 activation. On the basis of those findings, it is suggested that nimesulide and ibuprofen may offer protection in osteoarthritis through a non-COX-dependent effect such as the inhibition of apoptosis in chondrocytes.

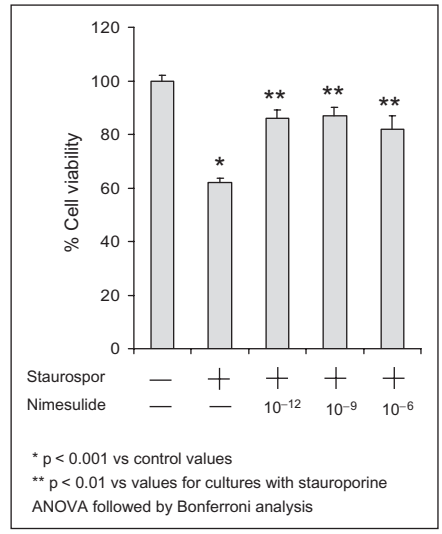

Fig. 5. Protective effect of nimesulide against staurosporine-mediated apoptosis of chondrocytes. **ANOVA** = Analysis of variance. Reproduced from Mukherjee et al.,[33] with permission. + and − represent the presence or absence of the agent indicated; i.e. staurosporine or nimesulide.

All of those studies demonstrated that the multifactorial mechanism of action of nimesulide, which goes beyond COX-2 enzyme inhibition, may have a beneficial impact on disease progression in rheumatology patients.

Conclusions

Differences exist between NSAIDs, particularly in terms of pharmacokinetic and pharmacodynamic properties. The therapeutic effect of these drugs derives mainly from their ability to inhibit COX-2; however, some NSAIDs exert their anti-inflammatory action via additional mechanisms.

Nimesulide, a preferential COX-2 inhibitor, has a multifactorial mechanism of action that affects the activity of MMPs and other biochemical markers of joint destruction, reduces the release of ROS and other toxic substances from neutrophils, and reduces the production of proinflammatory cytokines. These unique characteristics make nimesulide an appealing therapeutic choice in the development of new strategies in the treatment of rheumatology patients.

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