Introduction to "Nimesulide: Beyond COX-2"

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The sulfonanilide compound nimesulide (Fig. 1) is a proven nonsteroid anti-inflammatory drug (NSAID) that is anti-inflammatory, analgesic and antipyretic, and with a rapid onset of action. It has been appreciated since the early 1970s that NSAIDs have the common ability to block the formation of prostanoids via inhibition of cyclooxygenase (COX) (1). More recently it has become apparent that there are two COX isoforms: constitutively expressed COX-1, associated with the physiological production of prostanoids, and inducible COX-2, associated with the production of prostanoids at inflammatory sites (see 2). Studies *in vitro* (3, 4) and *ex vivo* (5, 6) have demonstrated that nimesulide is about 5-20 fold more potent an inhibitor of human cyclooxygenase-2 (COX-2) than of cyclooxygenase-1 (COX-1), possibly due to its ability to exploit the larger enzymatic channel in COX-2 allowing the formation of electrostatic interactions (7). This COX-2 selectivity supports the notion that at therapeutic doses nimesulide may spare the functional and protective prostaglandins formed by COX-1 in the gastric mucosa and kidney, while greatly inhibiting the formation by COX-2 of prostanoids involved in inflammation and pain (see 2). This may well provide at least some explanation for the finding that nimesulide causes relatively few adverse gastrointestinal and renal effects (8).

In addition to its effects on prostanoid formation, nimesulide may also produce a range of other beneficial anti-inflammatory effects. These include inhibition of the neutrophil oxidative response, reduction in the synthesis of cartilage-degrading enzymes, reduction of histamine action and release, inhibition of hyperalgesia caused by tumour necrosis factor- (see 9), reduction in the release of urokinase, interleukin-6 (10) and elastase (11), inhibition of the activity of collagenase (12) and depression of tumour necrosis factor- release (13). In addition, nimesulide may have direct blocking effects on calcium channels (14). It must be stated, however, that probably some of these effects are seen only at concentrations exceeding those achieved with therapeutic doses. On the other hand, as reported in these proceedings, there is very recent evidence that low concentrations of nimesulide can block the formation of COX-2 (15) and inhibit chondrocyte death (16). Therefore, in addition to its ability to block COX-2 selectively, other non-COX-dependent effects may underlie nimesulide's ability to produce positive therapeutic outcomes with relatively few side effects.

This relative safety and tolerability occurs in patients of all ages, even though the elderly are often treated simultaneously with several medicines, and even in patients with histories of adverse reactions to aspirin or other NSAIDs (17). Various studies have found that gastric mucosal damage by nimesulide is either similar to placebo or better than reference compounds (18, 19). Besides preferential COX-2 inhibition, a contribution to this gastrointestinal tolerability may be nimesulide's very weak acidity (pKa 6.5), which presumably reduces substantial accumulation in the gastric mucosa, and its minimal effect on oxidative phosphorylation.

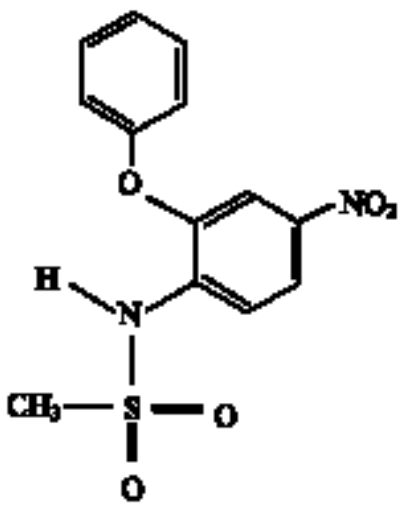

Fig. 1. Nimesulide.

Furthermore, very recent work has found that at the higher intragastric concentrations that might be obtained with oral doses, nimesulide inhibited murine gastric acid secretion induced by histamine or a stable acetylcholine analogue (20). Finally, the pharmacokinetics of nimesulide are similar in patients of all ages, and clinical problems relating to this aspect are few and of minor consequence (21).

In conclusion, nimesulide exhibits a range of actions that may underlie its efficacy in the treatment of pain, inflammation and fever, coupled with good gastrointestinal and renal safety and tolerability compared to other NSAIDs. This profile is reflected in nimesulide's exceptional market ranking at or near the top of the NSAID list in many countries.

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