Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen


Abstract

Background—Selective inhibitors of cyclooxygenase (COX)-2 may provoke less gastric damage and platelet inhibition than conventional non-steroidal anti-inflammatory drugs.

Aims—We compared the biochemical and gastrointestinal effects of nimesulide, a potent and selective COX-2 inhibitor, with naproxen which exhibits no selectivity.

Subjects—Thirty six healthy volunteers were randomised to nimesulide 100 mg or naproxen 500 mg twice daily for two weeks in a double blind, crossover study with a washout between treatments.

Methods—Gastrointestinal side effects were assessed by endoscopy, and by estimation of small intestinal absorption-permeability and inflammation. Comparisons were made between variables at the end of each treatment phase.

Results—Nimesulide caused significantly less gastric injury using the modified Lanza score (p<0.001) as well as reduced duodenal injury (p=0.039). Nimesulide had lower visual analogue scores (VAS) for haemorrhage and erosive lesions in the stomach (p<0.001) and for mucosal injection in the duodenum (p=0.039). Naproxen increased excretion of calprotectin, a marker of intestinal inflammation (5.5 (1.2) to 12.1 (2.1) mg/l) while nimesulide had no effect (treatment difference p=0.03). Naproxen abolished platelet aggregation to arachidonic acid and suppressed serum thromboxane B2 (TXB2) by 98%, indices of COX-1 activity. In contrast, nimesulide had no significant effect on platelet aggregation, although it reduced serum TXB2 by 29%. Production of prostaglandin E (PGE) and prostacyclin by gastric biopsies, also COX-1 dependent, was inhibited by naproxen, but not by nimesulide. COX-2 activity, determined as endotoxin induced prostaglandin E, formation in plasma, was markedly suppressed by both treatments.

Interpretation—Nimesulide has preferential selectivity for COX-2 over COX-1 in vivo at full therapeutic doses and induces less gastrointestinal damage than that seen with naproxen in the short term.

Keywords: cyclooxygenase; prostaglandins; platelet aggregation; non-steroidal anti-inflammatory drug enteropathy

Non-steroidal anti-inflammatory drugs (NSAIDs) are a major cause of iatrogenic gastrointestinal injury. Gastrointestinal toxicity is particularly evident in the stomach and duodenum, although injury occurs throughout the bowel. Cross sectional endoscopic studies in patients receiving NSAIDs show an ulcer prevalence of 10–25% with significant attendant mortality and morbidity. NSAIDs may also injure the small intestine, leading to a spectrum of damage from a change in permeability through to inflammation and ulceration, which may lead to anaemia and occasionally stricture formation.

NSAIDs are inhibitors of cyclooxygenase (COX) and prostaglandin (PG) formation. Two isoforms of the enzyme have been identified, COX-1 which is present in most cells, and COX-2 which is largely absent in normal tissue but is inducible by cytokines, growth factors, and hormones, and is expressed at the site of inflammation. COX-1 is largely responsible for PG formation in the stomach and duodenum, although COX-2 expression has been reported. COX-1 is the only form of the enzyme found in platelets. Inhibition of COX-1 in the stomach, where the major product is PGE, may be responsible in part for the injury seen with NSAIDs. Moreover, in experimental models, selective inhibition of COX-2 is associated with minimal or no gastrointestinal damage. Concomitant inhibition of COX-1 in platelets may also contribute to the haemorrhagic complications of gastrointestinal damage as this inhibits platelet thromboxane (TX) formation and aggregation, and prolongs bleeding time.

The majority of currently available NSAIDs inhibit both isoforms of the enzyme to a similar extent. An important development has been the identification of several compounds with selectivity towards COX-2. These compounds offer the potential for suppressing COX-2 at sites of inflammation while preserving COX-1 in the stomach and platelets. Consequently, COX-2 inhibitors may induce less gastric injury and haemostatic impairment. Here, we compare the gastrointestinal tolerability and in vivo biochemical selectivity of nimesulide, a relatively selective inhibitor of COX-2.

Abbreviations used in this paper: NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; PG, prostaglandin; TX, thromboxane; VAS, visual analogue score; LPS, lipopolysaccharide; PGI2, prostacyclin; ADP, adenosine diphosphate; TRAP, thrombin receptor activator peptide.

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Keywords: cyclooxygenase; prostaglandins; platelet aggregation; non-steroidal anti-inflammatory drug enteropathy
in vitro, with the non-selective COX inhibitor naproxen.

Subjects and methods

Subjects
Thirty six healthy volunteers, aged 40–67 years, were recruited from two centres, Beaumont Hospital Dublin, Ireland (n=13) and University Hospital Reykjavik, Iceland (n=23). Specific exclusion criteria were a past history of intolerance to NSAIDs, modified Lanza score of >1 at baseline endoscopy, past history of peptic ulcer disease, or any other clinically significant medical disorder. The ethics committees of the participating hospitals approved the study protocol and written informed consent was obtained from all subjects.

Study Design
At the start of period 1, subjects were randomly assigned to receive naproxen 500 mg twice daily and nimesulide placebo or nimesulide 100 mg twice daily and naproxen placebo for two weeks. The first period was followed by a two week washout and then subjects were assigned to the alternate therapies. The randomisation list was prepared using the software Rancode, v 3.1 (Gauting, Germany).

Gastrointestinal Evaluation
Endoscopic evaluation of subjects was performed at the start and end of each period. Gastric and duodenal damage was assessed separately using a modified Lanza score (tables 1, 2) and visual analogue score (VAS).

For the Lanza score, a score of 0 indicated no lesion, a single erosion or submucosal haemorrhage was given a score of 1, 2–10 erosions or submucosal haemorrhages a score of 2, >10 erosions or submucosal haemorrhages a score of 3, and an ulcer a score of 4. Lanza score 4 (“ulcer”) required an excavated mucosal break of 5 mm or more. For VAS scoring, the severity of two parameters, haemorrhagic and erosive lesions in the stomach and duodenum, was assessed along a linear 150 mm scale. Haemorrhagic lesions ranged from the presence of a few single petechiae to profuse bleeding in the stomach or duodenum, and erosive lesions from one erosion to frank ulceration.

The washout period was extended for up to four weeks if gastroduodenal damage had not returned to normal by the beginning of period 2. At each endoscopy, the presence of Helicobacter pylori was determined by the rapid urease activity assay (CLO test) and in four biopsy specimens, two each from the antrum and corpus by histology. All samples were stained with haematoxylin and eosin, a cresyl fast violet stain for H pylori, and GMori’s aldehyde fuchsin to identify intestinal metaplasia.

Gastritis was assessed according to a modified Sydney system which consists of a simple scoring system: absent=0, minimal=1, mild=2, moderate=3, and severe=4. The parameters scored were those associated with H pylori, chronic inflammation, acute inflammation, atrophy, and metaplasia. The highest possible total score was 20 for the antrum or corpus, but any score above 0 was regarded as abnormal.

Intestinal Absorption-Permeability

The 23 subjects from Iceland underwent a combined absorption-permeability test two days prior to and on day 10 of both the nimesulide and naproxen treatment periods, one hour following drug ingestion. All subjects abstained from alcohol and any medicines known to influence permeability and absorption. After an overnight fast, a test solution (100 ml of 3-α-methyl-D-glucose (0.2 g), D-xylose (0.5 g), L-rhamnose (1.0 g), and lactulose (5.0 g)) was administered orally and urine collected over five hours into 1 ml of 10% mercurithiosalicylate as preservative. Urinary sugars were determined by thin layer chromatography and scanning densitometry. The assay is sensitive, has 95% recovery, and a coefficient of variation of 2–8%.

This test assesses several small intestinal transcellular functions and paracellular integrity. 3-α-Methyl-D-glucose is absorbed by active carrier mediated process, D-xylose by a passive carrier mediated process, and L-rhamnose by a non-mediated transcellular transport system. Lactulose on the other hand permeates selectively across the paracellular junctions of the adjacent enterocytes. The differential urinary excretion of lactulose /L-rhamnose provides a specific index of intestinal permeability (intestinal barrier function). This permeability index is quite specific for mucosal function and is not significantly altered by pre- or post-gastric and intestinal dilution, gastric emptying, bacterial degeneration, etc or post-volume of distribution, renal function, etc mucosal factors that can effect urinary excretion of these markers following ingestion.

Intestinal Inflammation

Twenty three subjects in Iceland provided a stool specimen for measurement of calprotectin concentration (a non-degraded, neutrophil specific marker) on the same day as the intestinal absorption-permeability test. Samples of stool (20 g) were frozen and stored at −20°C. After thawing, 5 g aliquots were suspended in 10 ml of faecal extraction buffer (Tris buffered isotonic (150 mM) saline, 10 mM CaCl₂, and 0.25 mM thiomersal as antimicrobial agent, pH 8.4) and homogenised for one minute with an Ultra Turrax (Ika Werke, Germany) mechanical homogeniser. The homogenates were centrifuged at 10 000 g at +4°C. The top halves of the supernatants were pipetted off, frozen, and stored at −20°C until quantitation by ELISA. The normal range of faecal calprotectin excretion and concentration was established in 53 healthy volunteers (30 males, median age 36 years (range 18–60)) and in 36 patients with...
irritable bowel syndrome (10 men, median age 34 years (range 28–54)). Normal median calprotectin concentration was 3 mg/l with an upper limit (98% confidence limit) of 11 mg/l.

**EFFECT OF DRUGS ON COX-1 AND COX-2 ACTIVITY**

The effect of nimesulide and naproxen on COX-1 and COX-2 was assessed by several methods. Platelet aggregation and gastric mucosal PG generation were assessed in 13 Irish volunteers as a parameter of a COX-1 dependent process both before and during treatment with nimesulide and naproxen. In all 36 subjects, serum TXB₂ (reflecting COX-1 activity)²⁷ and lipopolysaccharide (LPS) induced PGE₂ synthesis (reflecting COX-2 activity)²⁸ in whole blood was measured both before and during treatment with nimesulide and naproxen.

**GASTRIC MUCOSAL PROSTANOID SYNTHESIS**

Prior to and on day 15 of treatment with nimesulide and naproxen in the 13 volunteers studied in Ireland, antral mucosal biopsies were obtained for determination of PGs (PGE₂, 6-keto-PGF₁α, a metabolite of prostacyclin (PGI₂)). Antral biopsies were incubated at 37°C for 45 minutes in 250 µl of phosphate buffered saline, and the supernatant stored at −20°C for subsequent analysis. PGE₂ was determined as maximum platelet aggregation at four different results in different periods. COX-2 activity was assessed by estimation of LPS induced PGE₂ formation in whole blood.²⁸ For analysis of PGE₂, 5 ml of whole blood were added to a tube containing a final concentration of aspirin 200 µM (to inactivate any COX activity) and LPS 1 µg/ml (to induce COX-2 expression) in water and incubated at 37°C for 24 hours. Samples were centrifuged for 10 minutes at 900 g and plasma stored at −20°C until analysed by ELISA (Assay Design), as described above.

**PLASMA DRUG LEVELS**

Plasma naproxen and nimesulide levels were determined one and two hours following administration of the last dose, corresponding to peak plasma drug levels. Plasma naproxen levels were determined by fluorometric detection following liquid-liquid extraction on the Merck-Hibar Lichrosorb RP18 using a mobile phase of 0.01 M phosphate pH 3 buffer, methanol, and acetonitrile acid (50/25/25 v/v/v). The limit of sensitivity was 0.5 µg/ml. Plasma nimesulide was determined by high performance liquid chromatography with UV detection. The limit of detection was 0.01 µg/ml.

**STATISTICAL ANALYSIS**

The sample size was determined for the primary outcome measure, the modified Lanza score. Based on the assumption that the Lanza score would increase above 1 in 65% of naproxen treated subjects and in 25% of those receiving nimesulide, a bimodal distribution for two paired group analysis was used to compute sample sizes. The rate of subjects giving different results in different periods (rate of switchers) was estimated by computing the probability of remaining normal (Lanza <1) on nimesulide and abnormal on naproxen and vice versa and was 57%. Using a two sided test difference, we estimated that at least 29 subjects would be required (α=0.05, β=0.1). Statistical analysis was on a per protocol basis as the design was crossover. A crossover analysis was performed taking in the baseline values and the final values for each period.

For the Lanza score data, two analyses were performed. A categorical analysis was performed where individuals were defined as normal (Lanza score ≤1) or abnormal (Lanza score >1). The number of subjects belonging to the four categories of possible (binomial) results (normal on naproxen but abnormal on nimesulide; normal on nimesulide but abnormal on naproxen; normal on both; abnormal on both) was assessed by the McNemar χ² test. In addition, the raw Lanza scores, VAS, and biochemical analyses were analysed using a Koch²⁵ test. Only the results from the analysis of treatment effects (which uses the Wilcoxon
matched pairs test) are presented here. As non-parametric tests have been used for statistical analysis, medians are presented throughout, although mean and standard errors are also presented for biochemical results. Friedman analysis for multiple comparisons within treatments has been used to identify changes from baseline for the naproxen and nimesulide groups separately.

**Table 1. Gastric damage scores (modified Lanza score): comparison of treatment effects of nimesulide and naproxen, and comparison of responders (Lanza score 0, 1) and non-responders (Lanza score >1)**

<table>
<thead>
<tr>
<th>Lanza score*</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Nimesulide Total naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Total nimesulide (%)</td>
<td>20 (57%)</td>
<td>5 (14%)</td>
<td>9 (26%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>35</td>
</tr>
<tr>
<td>Analysis of responders‡</td>
<td>Nimesulide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder (0, 1)</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder (2, 3, 4)</td>
<td>20</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNemar test: p&lt;0.001 (two sided).</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Modified Lanza score: 0, normal; 1, erosion or submucosal haemorrhage; 2, 2–10 erosions or submucosal haemorrhages; 3, >10 erosions or submucosal haemorrhage; 4, ulcer.
†Responder is a Lanza score of 0 or 1; a non-responder is a Lanza score of >1.

**Results**

Twenty four males and 12 females were recruited from the two centres. Demographic details and outcome measures were similar for the two centres and hence data from the two sites are presented jointly. The average age of subjects was 48 years (range 39–67). One male subject developed severe gastric damage at the end of the first treatment period where he had received naproxen, and as there was persistent ulceration four weeks later he was withdrawn from the study. As statistical analyses for crossover designs require patients to attend for more than one treatment period, this patient was omitted from these statistical analyses. Unless otherwise stated, data from 35 patients have been used for analyses.

**ENDOSCOPIC EVALUATION**

The results of the grading of gastrointestinal damage on the modified Lanza scale are shown in tables 1 and 2. One subject in the nimesulide group developed multiple (>10) gastric erosions and a separate subject developed a duodenal ulcer. By comparison, in the naproxen group, 16 developed multiple gastric erosions, four developed a gastric ulcer, three developed multiple duodenal erosions, and one a duodenal ulcer. Considering the main variable (rate of responders), the McNemar $\chi^2$ test (two sided) analyses of patients categorised as normal (Lanza score $\leq$1) or abnormal (Lanza score >1) showed that nimesulide was better tolerated than naproxen ($p<0.001$ in the stomach and $p=0.039$ in the duodenum). Examining the raw scores, the median treatment difference was $-2$ due to worse scores with naproxen. For the VAS (table 3, fig 1) of haemorrhagic lesions in the stomach, scores were greater (worse) with naproxen (median 50) compared with nimesulide (median 0). The difference between treatments was significant ($p<0.001$, Koch test, two sided). A similar result was evident for erosive lesions in the stomach ($p<0.001$), mucosal injection in the stomach ($p<0.001$), and mucosal injection in the duodenum ($p=0.038$). No treatment differences were evident when comparing haemorrhagic or erosive lesions in the duodenum. Comparison of Lanza scores for duodenal mucosal damage showed no difference (both median scores were zero, as was the median treatment difference).

Histological examination of the gastric biopsies showed that 19 of the 36 analysed subjects were positive for *H pylori* prior to the first treatment. This was found not to affect the baseline Lanza scores as the mean stomach score (averaged over the results for both treatments) was similar regardless of *H pylori* status (positive patients, mean 0.05 (0.05), median 0; negative patients, mean 0.29 (0.11), median 0). Moreover, the presence of *H pylori* did not influence the response to treatment.

**INTESTINAL ABSORPTION–PERMEABILITY AND INFLAMMATION**

Table 4 shows the results of the combined absorption-permeability tests. Neither treatment altered the absorption parameters (uri-
nary excretion of 3-o-methyl-D-glucose, D-xylose, L-rhamnose). Naproxen increased intestinal permeability as reflected by an increase in the differential urinary excretion of lactulose/L-rhamnose, whereas nimesulide had no such effect; however, the treatment difference was not statistically significant on day 10.

**INTESTINAL INFLAMMATION**
Calprotectin concentration was determined in the faeces of 23 subjects as a marker of intestinal inflammation. The change from baseline to day 10 showed a significant treatment effect (p=0.03). Nimesulide had no effect over the 10 days (6.1 (2.3) mg/l (range 0.5–55.0) v 6.9 (1.3) mg/l (range 0.5–25)) whereas naproxen increased calprotectin excretion (5.5 (1.2) mg/l (range 0–25) v 12.1 (2.1) mg/l (range 0–43)).

**EICOSANOIDS GENERATION**
PGE$_2$ and PGI$_2$ (measured as 6-keto PGF$\text{\textsubscript{1}}$\text{\textalpha}) generation by gastric biopsy was similar to that reported previously.$^{40}$ Generation of both products was markedly reduced by naproxen but not by nimesulide and there was a significant difference between treatments (p<0.01) (fig 2). Serum TXB$_2$ was markedly inhibited by naproxen, falling by 98% throughout the treatment period. For nimesulide, there was a small decrease from baseline to day 3 (273 (13) v 180 (15) ng/ml) which resulted in an average decrease of 29% throughout the treatment period (treatment effect was p<0.001 for the change from baseline to day 10) (fig 3A). LPS induced PGE$_2$ in plasma, which reflects COX-2 activity, was evaluated in 33 subjects. Plasma PGE$_2$ decreased by 74% on naproxen, less than the 93% reduction seen with nimesulide (p=0.053 for the change from baseline to day 10) (fig 3B).

**PLATELET AGGREGATION**
A total of 13 patients were analysed for platelet aggregation, although due to missing data, values from 7 to 12 patients are available when changes from baseline are considered. Figure 4 shows that arachidonic acid induced platelet aggregation, which is dependent on COX-1 mediated TXA$_2$ formation, was largely unaffected by nimesulide. In contrast, there was marked suppression of arachidonic acid induced platelet aggregation throughout administration of naproxen (Friedman analysis p<0.001 on days 3, 10, and 15). Treatment

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Nimesulide</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-o-methyl-D-glucose (%)</td>
<td>46 (2.9) [45]</td>
<td>41 (2.2) [44]</td>
</tr>
<tr>
<td>D-xylose (%)</td>
<td>28 (1.5) [28]</td>
<td>27 (1.2) [26]</td>
</tr>
<tr>
<td>L-rhamnose (%)</td>
<td>8.4 (0.5) [8.5]</td>
<td>8.0 (0.4) [8.0]</td>
</tr>
<tr>
<td>Lactulose/L-rhamnose</td>
<td>0.028 (0.0) [0.023]</td>
<td>0.027 (0.0) [0.029]</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>46 (2.2) [47]</td>
<td>41 (2.4) [42]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>29 (1.3) [30]</td>
<td>27 (1.6) [28]</td>
</tr>
<tr>
<td>Lactulose/L-rhamnose</td>
<td>0.032 (0.01) [0.025]</td>
<td>0.042 (0.01) [0.034]</td>
</tr>
</tbody>
</table>

*p Value* *Koch test, treatment effect.
References (from baseline) were analysed on day 10 and showed a significant ($p=0.048$) effect. Platelet aggregation to ADP, where the secondary wave of aggregation is TXA2 dependent, was not significantly altered by nimesulide but was inhibited by naproxen ($p<0.01$ days 3 and 15). No significant treatment differences were evident on day 10.

Nimesulide had no effect on TRAP induced platelet aggregation, which is independent of TXA2 formation. Similarly, TRAP induced platelet aggregation was largely unaffected by naproxen, although a small degree of inhibition was noted on day 15. No treatment difference was evident on day 10.

PLASMA LEVEL OF NIMESULIDE AND NAPROXEN

Following the last dose, plasma concentrations of nimesulide were 5.4 (0.4) (range 0.13–11.4) µg/ml at one hour and 5.5 (0.3) (range 3.1–8.2) µg/ml at two hours, falling to 4.2 (0.3) (range 1.2–7.8) at four hours. Corresponding naproxen plasma levels were 70 (4) (range 22–110), 86 (4) (range 20–127), and 6.4 (2) (range 18–91) µg/ml. Plasma concentrations fell to undetectable levels for both drugs within 48 hours of discontinuation.

Discussion

Gastric and small intestinal damage is common in short and long term users of NSAIDs. NSAID induced gastroduodenal ulceration is associated with life threatening bleeding or perforation in an estimated 1 in 5000–20 000 prescriptions.41 NSAID induced enteropathy may manifest as iron deficiency anaemia, hypoalbuminaemia due to protein loss,10 and rarely as small and large intestinal strictures.42 The mechanism of NSAID induced injury is thought to reflect, at least in part, inhibition of cyclooxygenase and loss of cytoprotective prostaglandins, although a direct “topical effect” may also play a role.1

Here, we examined the degree of gastroduodenal and small intestinal injury with nimesulide, a relatively selective COX-2 inhibitor during short term administration of the drug. Short term studies are thought to over represent erosive damage by NSAIDs compared with long term studies. However, they are suitable for the purpose of examining the effect of inhibiting COX as they avoid the confounding effect of “adaptation” whereby the damaging effects of COX inhibition is over-

Figure 3 (A) Comparison of the effects of nimesulide and naproxen on serum thromboxane B$_2$ (TXB$_2$) (a measure of COX-1 activity) before and during treatment with nimesulide 100 mg twice daily or naproxen 500 mg twice daily. Data are shown as mean (SEM). Naproxen had a greater effect on serum TXB$_2$ ($p<0.001$ for comparison between treatments to day 10). Note that nimesulide reduced serum TXB$_2$ on average by 29% from baseline ($p<0.01$) and that both drugs markedly reduced plasma PGE$_2$. (B) Plasma prostaglandin (PG) E$_2$ (a measure of COX-2 activity). Nimesulide had a slightly greater effect on plasma PGE$_2$ ($p=0.053$ for comparison between treatments to day 10).

Figure 4 Comparison of the effects of nimesulide and naproxen on platelet aggregation to arachidonic acid (A), adenosine diphosphate (ADP) (B), and thrombin receptor activator peptide (TRAP) (C) before and during treatment with nimesulide 100 mg twice daily or naproxen 500 mg twice daily. Data are shown as mean (SEM). **$p<0.01$, ***$p<0.001$ for changes from baseline; †$p=0.048$ for comparison between treatments.
come in time. The range and prevalence of the gastroduodenal damage by naproxen was in keeping with that previously described.\textsuperscript{44-45} By comparison, gastric damage by nimesulide was significantly less and 71% of patients remained within Lanza 0–1. This degree of gastric tolerability was similar to that described with the highly selective COX-2 inhibitors celecoxib\textsuperscript{46} and rofecoxib.\textsuperscript{47}

As reported previously with NSAIDs,\textsuperscript{48} duodenal damage was less marked than gastric damage and again was significantly less with nimesulide that naproxen. Nevertheless, a duodenal ulcer was found in a single subject on nimesulide who was positive for \textit{H pylori.} Parenthetically, \textit{H pylori} infection had no synergistic effect on damage caused by either drug in this study although this has been reported previously.\textsuperscript{49}

Increased permeability of the small intestine has been documented with most conventional NSAIDs.\textsuperscript{50} In this study, nimesulide failed to alter intestinal permeability, in keeping with animal studies.\textsuperscript{49} In contrast, naproxen increased intestinal permeability, as shown previously in humans.\textsuperscript{51} To date, all NSAIDs that increases intestinal permeability are associated with a high prevalence (40–65%) of NSAID enteropathy, measured as excretion of calprotectin.\textsuperscript{52} Not surprisingly then, naproxen but not nimesulide increased intestinal inflammation. Although it has been suggested that inflammation may be delayed for six months,\textsuperscript{53} it has been reported earlier,\textsuperscript{54} in keeping with our study.

The improved gastrointestinal tolerability of nimesulide is consistent with its relative COX-2 selectivity and maintenance of gastric prostaglandin formation. As a measure of gastric COX activity, we examined generation of PGs in gastric mucosal biopsies. Nimesulide did not alter formation of either PGE\textsubscript{2}, or PGI\textsubscript{2}, in the stomach. PGE\textsubscript{2} is the major product of gastric epithelial cells.\textsuperscript{19} However PGE\textsubscript{2} is also generated by platelets so that any inhibitory effect of an NSAID could be due to inhibition of platelets contaminating the biopsies. To address this issue, we measured 6-keto-PGF\textsubscript{1\alpha}, a metabolite of PGI\textsubscript{2}. PGI\textsubscript{2} is generated by nucleated cells, such as gastric epithelial and vascular endothelial cells.\textsuperscript{54} Naproxen inhibited both products whereas nimesulide had little effect on gastric PGE\textsubscript{2}, or 6-keto-PGF\textsubscript{1\alpha}, at a time when there were substantial levels of the drug in blood.

Studies in whole blood allowed us to compare the relative selectivity of the two compounds for the COX isomers. Serum TXB\textsubscript{2}, a measure of COX-1 activity of platelets,\textsuperscript{55} is highly sensitive to inhibition as platelets are incapable of regenerating new enzyme. Nimesulide inhibited serum TXB\textsubscript{2} by about 30% over the period of the study, as has been reported with the highly selective COX-2 inhibitor celecoxib.\textsuperscript{56} However, it is unlikely that this modest effect would alter haemostatic function, as very marked (>95%) inhibition of platelet COX-1 is required to suppress platelet aggregation.\textsuperscript{57} Indeed, platelet aggregation to arachidonic acid and ADP, which is TXA\textsubscript{2} dependent, was preserved.

As a marker of a COX-2 effect, we used an assay developed by Punnonen and colleagues\textsuperscript{58} in which COX-2 in monocytes is induced by LPS, resulting in PGE\textsubscript{2}, formation. Both drugs suppressed PGE\textsubscript{2}, formation resulting from LPS treatment. This relative selectivity of nimesulide for COX-2 demonstrated in vivo is consistent with the selectivity seen in vitro at peak plasma levels achieved (∼18 µM and 98% protein bound).\textsuperscript{57}

In summary, nimesulide causes less endoscopic and functional evidence of gastrointestinal injury compared with naproxen. This is consistent with our findings showed that nimesulide is a selective COX-2 inhibitor in vivo, with little effect on haemostatic function or gastric prostaglandin formation. A critical issue is whether the short term endoscopic benefits seen with a selective COX-2 inhibitor such as nimesulide translate into a more long term benefit, particularly a reduction in bleeding and perforation. In addition, it remains to be seen if an anti-inflammatory effect will ensue from COX-2 inhibition alone, in that COX-1 has been implicated in some models of inflammation. Indeed, in a mouse model of inflammation, Wallace and colleagues reported a significant reduction in inflammation with nimesulide but only at doses that also inhibited COX-1.\textsuperscript{57}

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