Importance of local versus systemic effects of non-steroidal anti-inflammatory drugs in increasing small intestinal permeability in man

I Bjarason, B Fehilly, P Smethurst, I S Menzies, A J Levi

Abstract

Increased small intestinal permeability caused by non-steroidal anti-inflammatory drugs (NSAIDs) is probably a prerequisite for NSAID enteropathy, a source of morbidity in patients with rheumatoid arthritis. This increased small intestinal permeability may be a summation of a local effect during drug absorption, a systemic effect after absorption, and a local effect of the drug excreted in bile, but the relative contribution made by these factors is unknown. We assessed the effect of indomethacin and nabumetone on intestinal permeability. The principal active metabolite of nabumetone, 6-methoxy-2-naphthylacetic acid, is not subject to appreciable enterhepatic recirculation. Twelve volunteers were studied before and after one week's ingestion of indomethacin (150 mg/day) and nabumetone (1 g/day) with a combined absorption/permeability test. Neither drug had a significant effect on the permeation of 3-0-methyl-D-glucose, D-xylene, and L-rhamnose. Indomethacin increased the permeation of radioactively labeled ethylenediamine-N,N,N',N'-tetra-acetic acid (14Cr EDTA) significantly from baseline (mean (SEM) 0-63 (0-09)% v 1-20 (0-14)% p<0-01) but nabumetone did not (0-70 (0-10)% p>0-1). These results were supported by the 14Cr EDTA/L-rhamnose urine excretion ratios, which reflect changes in intestinal permeability. They suggest that NSAIDs increase intestinal permeability during absorption or after biliary excretion and that the systemic effect is of minor importance.

Subjects and methods

Twelve volunteers (six men and six women; mean (SD) age 29 (2) years) participated in this randomised, double blind study. After an overnight fast each ingested a 100 ml test solution (105 mOsm/l) containing: 3-0-methyl-D-glucose (0-2 g); D-xylene (0-5 g); L-rhamnose (1-0 g); radioactive 14Cr ethylenediamine-N,N,N',N'-tetra-acetic acid (100 μCi, 3-7 MBq). These probes are thought to assess predominantly active and passive carrier mediated transport and trans- and paracellular permeation, respectively.6,10

Urine was collected for five hours into a plain bottle containing 1 ml (10% w/v) mercurithiosalicylate (thimersol) as preservative for marker analysis as described.8

Volunteers were tested as follows:

(a) As control subjects;
(b) After taking indomethacin (50 mg×3) for seven days;
(c) After taking nabumetone (1·0 g) at midnight for seven days.

The amounts of indomethacin and nabumetone chosen were the recommended maximum daily doses in clinical practice and have been shown to be of similar efficacy in patients with rheumatoid arthritis.11,12 After each test there was a 10 day wash out period before beginning the next. On day 7, in between treatments, subjects underwent a permeability test involving...
Percentage five hour urinary excretion of four test substances

<table>
<thead>
<tr>
<th></th>
<th>3-0-m glucose</th>
<th>D-xylose</th>
<th>L-rhamnose</th>
<th>¹⁸Cr EDTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean (SEM))</td>
<td>48.8 (4.0)</td>
<td>30.5 (2.4)</td>
<td>17.4 (2.5)</td>
<td>0.63 (0.09)</td>
</tr>
<tr>
<td>Range</td>
<td>(22.3 - 67.3)</td>
<td>(12.5 - 42.1)</td>
<td>(4.7 - 30.9)</td>
<td>(0.13 - 1.21)</td>
</tr>
<tr>
<td>Indomethacin (mean (SEM))</td>
<td>51.5 (3.1)</td>
<td>33.4 (2.3)</td>
<td>14.6 (1.3)</td>
<td>1.20 (0.14)</td>
</tr>
<tr>
<td>Range</td>
<td>(38.2 - 69.2)</td>
<td>(23.0 - 51.9)</td>
<td>(8.4 - 20.5)</td>
<td>(0.40 - 1.81)</td>
</tr>
<tr>
<td>Nabumetone (mean (SEM))</td>
<td>50.1 (2.6)</td>
<td>32.9 (2.1)</td>
<td>14.9 (1.4)</td>
<td>0.70 (0.10)</td>
</tr>
<tr>
<td>Range</td>
<td>(29.8 - 62.1)</td>
<td>(23.2 - 49.3)</td>
<td>(9.1 - 22.9)</td>
<td>(0.26 - 1.41)</td>
</tr>
</tbody>
</table>

* Differs significantly from baseline (p<0.01).

the ingestion of a 300 ml test solution of L-rhamnose (0.5 g) and ¹⁸Cr EDTA followed by a five hour urine collection for marker analysis.

On the days 3 and 8 of ingestion of indomethacin or nabumetone, serum was taken to ensure drug compliance. Plasma was assayed for indomethacin or 6 MNA, which is the major active component of nabumetone as described.²³ ²⁴

All subjects gave informed consent to the studies, which were approved by the Harrow Health Authority Ethical Committee.

Two way analysis of variance was used to assess statistical significance.

Results
The Table shows that the percentage urine excretions of 3-0-methyl-D-glucose, D-xylose, and L-rhamnose did not differ significantly from control values after taking indomethacin or nabumetone. The urine excretion of ¹⁸Cr EDTA increased significantly after taking indomethacin but not after nabumetone. The Figure shows that the ¹⁸Cr EDTA results were mirrored by changes in the ¹⁸Cr EDTA:L-rhamnose urine excretion ratios, which specifically reflect changes in intestinal permeability.

The ¹⁸Cr EDTA:L-rhamnose permeability tests that were performed in the washout period seven days after the last dose of indomethacin and nabumetone showed normal excretion ratios in all cases.

Serum analyses for indomethacin and 6 MNA on days 3 and 8 showed compliance in all cases.

Discussion
This study shows that a week's ingestion of indomethacin causes a selective increase in the permeation of ¹⁸Cr EDTA. Nabumetone, on the other hand, had no appreciable effect on intestinal permeability. Given that the doses administered, which are the maximum recommended doses, have similar efficacy in patients with rheumatoid arthritis, the results suggest that the systemically mediated effect of NSAIDs is relatively weak and the main damage is sustained during drug absorption or after the drug's excretion in bile. We have also shown that the effect of indomethacin is short lived, with restoration of intestinal integrity within a week of the last ingested dose. This contrasts with that seen in NSAID enteropathy where inflammation may persist for over 16 months after stopping NSAIDs.²¹

The advantages of using a combined absorption permeability test is that the results can be interpreted more specifically and accurately.²⁴ ²⁷

Thus, the urine excretion of a single test substance after ingestion is affected by preabsorptive factors (gastrointestinal dilution and emptying, intestinal dilution and transit), mucosal permeability, blood flow, and postmucosal factors (metabolism, renal handling) so that changed urine excretion could be due to an alteration in any of a number of factors. When the test is a combined one, however, it is clear that a change in a pre- or postmucosal factor(s) will affect both markers to a similar extent so that the urine excretion ratio will not be affected. Damage to the mucosa, however, is unlikely to affect all four permeation pathways equally and in practice is usually manifested as reduced permeation of the monosaccharides and increased permeation of ¹⁸Cr EDTA, reflecting potential malabsorption and disruption of the intestinal barrier function respectively.²⁵

The increased intestinal permeability to ¹⁸Cr EDTA after taking indomethacin localises the damage to the intercellular occluding junction of adjacent enterocytes, which is the main barrier to the permeation of ¹⁸Cr EDTA and hydrophilic macromolecules. The precise mechanism by which NSAIDs cause this damage is uncertain but we have previously shown that the permeability changes relate to NSAID ability to inhibit cyclo-oxygenase²² and are partially reversed by concomitant prostaglandin administration.²³ This suggests that the effect is partly due to reduced mucosal prostaglandin production, perhaps with diversion of arachidonic acid into the lipo-oxygenase pathway resulting in increased leukotrienes that may cause damage by free oxygen radical production and microvascular vasconstriction.²⁴ In addition, NSAIDs reduce...
cellular adenosine triphosphate production by inhibiting steps in glycolysis and the tricarboxylic acid cycle. It is suggested that together these actions affect the enterocyte in such a way that it fails to maintain the energy dependent intracellular mechanism that regulates and controls the integrity of the intercellular junction and hence the increased permeation of C" EDTA.

This study suggests that a high local concentration of an active NSAID, either after ingestion or biliary excretion, is necessary to increase small intestinal permeability and that the systemic effect is relatively unimportant. The recent trend of a shift from NSAID tablets to capsules or incorporation of NSAIDs into slow release or sustained release preparations in the hope of circumventing their local gastroduodenal irritancy, may therefore inadvertently increase the frequency of small intestinal damage.

The consequences of increased intestinal permeability are that the mucosa may be exposed to substances such as luminal toxins, bile acids, pancreatic juices, and bacterial and food derived macromolecules. Over the months this may allow bacterial invasion of the mucosa with resultant neutrophil chemotaxis as seen with radioactive indium labelled leukocytes. On phagocytosis of bacteria, the neutrophils may cause tissue damage by free oxygen radical production and lysosomal release, which in turn causes bleeding and small intestinal protein loss. As the permeability changes seem to be a prerequisite for NSAID enteropathy, further long term studies are required to assess whether nabumetone reduces the frequency and severity of these. Whether patients with established NSAID enteropathy would benefit from a change in their NSAID is less certain and also requires study as the systemic effect of 6 MNA, although insufficient to initiate damage, may be sufficient to perpetuate the disease.

Thanks to Beecham Pharmaceuticals for the supply of drugs.