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

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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 enterohepatic 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-xylose, and L-rhamnose. Indomethacin increased the permeation of radioactive ^{51}chromium ethylenediaminetetra-acetic acid (^{51}Cr 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 ^{51}Cr 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.

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It is generally thought the the gastroduodenal mucosa bears the main brunt of non-steroidal anti-inflammatory drug (NSAID) related gastrointestinal side effects.[1–3] While this may be true for the serious side effects of haemorrhage and perforation,[4 5] it is becoming increasingly clear that it is the small intestine that is most frequently affected by NSAIDs.[6] Thus, 60–70% of patients who take NSAIDs for more than six months have small intestinal inflammation.[7–9] The inflammation is important because it is associated with the complications of small intestinal bleeding and protein loss[10] and the diaphragmatic like small intestinal strictures caused by NSAIDs that occasionally affect patients and may require surgery.[11 12]

The pathogenesis of NSAID enteropathy has been the subject of much study. Within hours of NSAID ingestion there is an increase in intestinal permeability and it is suggested that the mucosa is thereby exposed to endo- and exogenous luminal toxins. If NSAIDs are taken for over six months a bacterial infection sets in leading to neurophil chemotaxis.[6]

Increased small intestinal permeability caused by NSAIDs can be viewed as a summation of three events[13] – NSAIDs can exert their effect on the small intestine during absorption, after absorption as a part of the systemic effect, and thirdly through re-exposure of the small intestine after the drugs' biliary excretion. The relative importance of each event, however, is unknown. We have assessed the effect of indomethacin and nabumetone on small intestinal permeability. Because nabumetone is a pro-NSAID, it is a poor inhibitor of prostaglandin synthesis until it is converted into its active form, 6-methoxy-2-naphthylacetic acid (6 MNA), when it becomes a potent NSAID.[14] Nabumetone would therefore have little effect on the mucosa during its absorption phase, and as it is not secreted significantly into the bile it would also have little effect via this route.[15] Thus, if this NSAID showed any action on the gut, it would occur after its conversion into its active form via the systemic circulation.

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-xylose (0·5 g); L-rhamnose (1·0 g); radioactive ^{51}chromium ethylenediaminetetra-acetic acid (^{51}Cr EDTA) (100 μCi, 3·7 mBq). These probes are thought to assess predominantly active and passive carrier mediated transport and trans- and paracellular permeation, respectively.[16–20]

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.[16]

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.[21 22] 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

	3-O-m glucose	D-xylose	L-rhamnose	^{51}Cr EDTA
Baseline (mean (SEM))	48·8 (4·0)	30·5 (2·4)	17·4 (2·5)	0·63 (0·09)
(Range)	(22·3 – 67·3)	(12·5 – 42·1)	(4·7 – 30·9)	(0·13 – 1·21)
Indomethacin (mean (SEM))	51·5 (3·1)	33·4 (2·3)	14·6 (1·3)	1·20 (0·14)*
(Range)	(38·2 – 69·2)	(23·0 – 51·9)	(8·4 – 20·3)	(0·40 – 1·81)
Nabumetone (mean (SEM))	50·1 (2·6)	32·9 (2·1)	14·9 (1·4)	0·70 (0·10)
(Range)	(29·8 – 62·1)	(23·2 – 49·3)	(9·1 – 22·9)	(0·26 – 1·41)

* Differs significantly from baseline ($p<0·01$).

the ingestion of a 300 ml test solution of L-rhamnose (0·5 g) and ^{51}Cr 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 ^{51}Cr EDTA increased significantly after taking indomethacin but not after nabumetone. The Figure shows that the ^{51}Cr EDTA results were mirrored by changes in the ^{51}Cr EDTA:L-rhamnose urine excretion ratios, which specifically reflect changes in intestinal permeability.

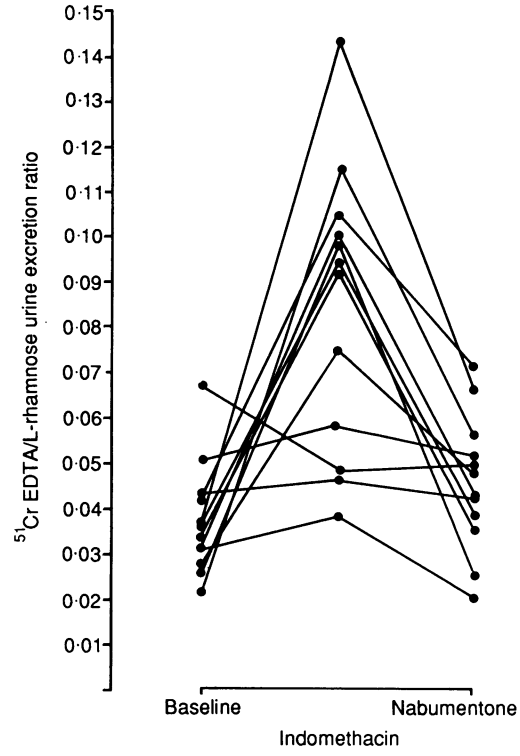
The ^{51}Cr EDTA/L-rhamnose permeability tests that were performed in the washout period seven days after the last dose of indomethacin and nabumetone showed normal excretion ratios in all cases.

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 ^{51}Cr 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.[7]

The advantages of using a combined absorption permeability test is that the results can be interpreted more specifically and accurately.[16 17]



Five hour urinary excretion ratio of ^{51}Cr EDTA:L-rhamnose. Indomethacin increased the ^{51}Cr EDTA:L-rhamnose excretion ratio significantly from baseline (mean (SEM), 0·088 (0·008) and 0·037 (0·003) respectively $p<0·01$) but nabumetone did not (0·046 (0·005) $p>0·05$).

Thus, the urine excretion of a single test substance after ingestion is affected by premucosal (gastric 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 ^{51}Cr EDTA, reflecting potential malabsorption and disruption of the intestinal barrier function respectively.[17 25]

The increased intestinal permeability to ^{51}Cr EDTA after taking indomethacin localises the damage to the intercellular occluding junction of adjacent enterocytes, which is the main barrier to the permeation of ^{51}Cr 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-oxygenase[26] and are partially reversed by concomitant prostaglandin administration.[27] 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 microvasculature vasoconstriction.[28] In addition, NSAIDs reduce

cellular adenosine triphosphate production by inhibiting steps in glycolysis and the tricarboxylic acid cycle.[29] 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[30] and hence the increased permeation of ^{51}Cr 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,[31 32] 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.

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