

Alimentary tract and pancreas

Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine

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SUMMARY Intestinal permeability was estimated in healthy subjects after ingestion of aspirin (1.2+1.2 g), ibuprofen (400+400 mg) and indomethacin (75+50 mg) at midnight and an hour before starting a ⁵¹chromium labelled ethylenediaminetetraacetate absorption test. Intestinal permeability increased significantly from control levels following each drug and the effect was related to drug potency to inhibit cyclooxygenase. Intestinal permeability increased to a similar extent after oral and rectal administration of indomethacin showing that the effect is systemically mediated. Prostaglandin E₂ decreased intestinal permeability significantly but failed to prevent the indomethacin induced increased intestinal permeability. These studies show that non-steroidal anti-inflammatory drugs disrupt the intestinal barrier function in man and suggest that the morphological correlates of the damage may reside at the level of the intercellular junctions.

Several non-steroidal anti-inflammatory drugs (NSAIDs) induced characteristic intestinal damage in various animal species.¹ This is particularly severe in the rat where subcutaneous indomethacin leads to small bowel inflammation with ulceration, perforation, and ultimately death within 72 hours.²⁻⁵ The precise mechanism underlying this sequence of events is unknown but there is substantial data to implicate both reduced synthesis of mucosal prostaglandins and the presence of intestinal bacteria in the pathogenesis of the lesions.^{6,7} Thus the macroscopic damage is preceded by a period of profound inhibition of mucosal cyclooxygenase activity⁸ and damage can be prevented by the simultaneous administration of a variety of prostaglandins.^{5,9,10} The role of intestinal bacteria is suggested by findings that intestinal ulceration after NSAIDs is rarely seen in germ free animals and the damage is greatly reduced after the coadministration of various antibiotics by a mechanism which appears to differ from their 'cytoprotective' properties.^{11,12}

Until recently the human small intestine was thought to be relatively unaffected by NSAIDs.

During studies into the importance of altered intestinal permeability in the pathogenesis of rheumatoid arthritis it was shown that NSAID treatment was associated with increased intestinal permeability to ⁵¹Chromium labelled ethylenediaminetetraacetate (⁵¹CrEDTA).¹³ Further studies showed that long term NSAID treatment leads to distinct migratory abnormalities of ¹¹¹indium labelled leucocytes to the ileum indicating small bowel inflammation.¹³ Together with evidence of increased faecal ¹¹¹indium excretion, which is a specific and objective index of intestinal inflammation,¹⁴ it is now clear that NSAIDs cause small bowel inflammation in a substantial number of patients receiving these drugs.¹⁵ With reference to the animal model it seems possible that the increased absorption of ⁵¹CrEDTA, which precedes the scan abnormality, reflects loss of intestinal integrity because of decreased prostaglandin production and the inflammation itself reflects a response to a bacterial invasion. Our purpose was thus to assess whether NSAID induced increased intestinal permeability in man relates to drug potency to inhibit cyclooxygenase, whether the permeability change is due to a direct irritant or a systemically mediated effect of the drugs. In addition the effect of indomethacin on the glomerular filtration rate was investigated as pre-

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Received for publication 21 February 1986.

vicious studies on this phenomenon were controversial,¹⁶⁻²⁰ and alterations in glomerular filtration rate might be expected to affect the urinary excretion of ⁵¹CrEDTA. Finally we studied whether the increased intestinal permeability could be prevented by exogenous administration of prostaglandin since, if successful, it could have direct therapeutic implications for the prevention of intestinal inflammation.

Methods

SUBJECTS

Fourteen healthy white volunteers, age range 26-39 years, took part in these studies. On separate occasions intestinal permeability was estimated by the ⁵¹CrEDTA absorption test in 10 subjects: (A) baseline, (B) after aspirin (1.2+1.2 g), (C) after ibuprofen (400+400 mg), (D) after indomethacin (75+50 mg).

These NSAIDs, listed in order of increasing potency to inhibit cyclooxygenase,^{21 22} were administered at midnight and an hour before study in the quantities indicated.

Six of these subjects on a different occasion received rectally an indomethacin (100 mg) suppository an hour before study.

Glomerular filtration rate was measured in four subjects as baseline and after 75 mg indomethacin at midnight and 50 mg an hour before study.

Seven subjects carried out the ⁵¹CrEDTA absorption test: (i) Baseline, (ii) After indomethacin (75 mg+50 mg at -8 and -1 h), (iii) After prostaglandin E₂ (Prostin E₂; Upjohn), (1 mg at -14, -8, -1, +5, +11 h), (iv) After both (ii) and (iii), (v) After ranitidine (150 mg at -24, -12, -1, +12 h) and (iv).

The permeability estimations were done at least six days apart and in no particular order. Preliminary studies had shown that the effect of the drugs when given in these doses was not evident 48 hours after administration. Each subject abstained from alcohol for at least a week before study.²³

PERMEABILITY MEASUREMENTS

The test solution consisted of 100 µCi (3.7 MBq) of ⁵¹CrEDTA (Amersham International, Amersham, Buckinghamshire, Code J13P) in 10 ml distilled water.²³ At 8 am, after an overnight fast, subjects drank the test solution followed by approximately 300 ml water and were allowed normal food and fluid intake two hours later. Urine was collected for 24 hours after ingestion of the test solution, made up to 2 litres in polyethylene bottles and counted for 100 seconds in a bulk sample counter along with appropriate standards.²⁴ The minimal detectable

activity of ⁵¹CrEDTA is less than 0.001% of the orally administered dose. The precision of the urine counting (coefficient of variation) is less than 1%.

GLOMERULAR FILTRATION RATE MEASUREMENTS
Subjects received 5 ml (70 µCi) of ⁵¹CrEDTA intravenously at 9 am after an overnight fast. Blood samples were taken at five and 15 min and thereafter hourly for seven hours. Four millilitres serum was counted in a Wallac 1280 gamma counter along with 4 ml 1/500 dilution of the original. The coefficient of variation for this counting procedure is less than 1%. Glomerular filtration rate and the extracellular (⁵¹CrEDTA distribution) volume were calculated using a computer program based on the principles outlined by Veall and Gibbs²⁵ and subsequently validated by Watts *et al.*^{26 27}

The paired Student's *t* test was used for statistical analysis.

These studies were approved by the Harrow Health Authority Ethical Committee.

Results

For the control test A (n:10) the mean (±SD) 24 hour urine excretion of ⁵¹CrEDTA was 1.9±0.5% (range 1.0-2.6%). There was a significant and stepwise increase in excretion values after ingestion of the NSAIDs in accordance with their potency to inhibit cyclooxygenase (Test B, C, D). Thus the urine excretion of ⁵¹CrEDTA increased after aspirin (n:6) to 2.3±0.3% (range 1.3-3.4%, p<0.05), ibuprofen (n:10) 2.9±1.2% (range 1.6-5.6%, p<0.001) and indomethacin (n:10) to 4.7±1.3% (range 2.9-7.2%, p<0.001).

The urine excretion of ⁵¹CrEDTA after rectal administration of indomethacin, 4.5±0.9% (range 3.3-5.8%), differed significantly (p<0.001) from that of control levels but not from that obtained when indomethacin was ingested.

Indomethacin decreased glomerular filtration rate significantly (p<0.01) from baseline values of 137, 140, 105, 118 ml/min to 127, 130, 93 and 104 ml/min which is a reduction of 8, 7, 11 and 12% respectively. There was no significant change in the distribution space of ⁵¹CrEDTA (extracellular volume) before and after indomethacin (18.9±3.3 and 18.5±2.9 l respectively).

The Figure shows the results after ingestion of prostaglandin E₂ and indomethacin. Baseline 24 hour urine excretion of ⁵¹CrEDTA (n:7) was 2.2±0.6%. Prostaglandin administration (n:7) decreased the 24 hour excretion modestly but significantly to 1.5±0.7% (p<0.01), while indomethacin (n:7) increased the excretion to 4.6±1.5% (p<0.001). The administration of prostaglandin E₂ before, with

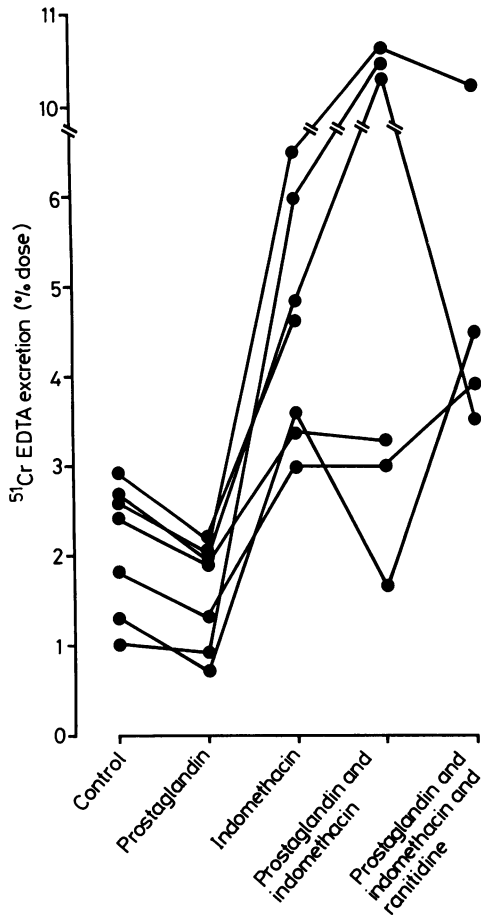


Figure The 24 hour urine excretion of ^{51}Cr -ethylenediaminetetraacetate after prostaglandin E_2 and indomethacin ingestion.

and after indomethacin (n:6) did not prevent the indomethacin induced increased intestinal permeability; urine excretion $6.6 \pm 4.4\%$, nor was there a significant change when gastric acid secretion was decreased with ranitidine in the four subjects studied, urine excretion $5.6 \pm 3.2\%$.

Discussion

The beneficial effects of NSAIDs in the treatment of rheumatic and related arthropathies is coupled with the inescapable risk that they frequently cause untoward effects. The most common side effects relate to the gastrointestinal tract in the form of abdominal pain, nausea, heart burn and dyspepsia.²⁸ The cause for these symptoms is often unknown

although in a proportion of patients these are attributed to gastritis or aggravation of peptic ulcer disease. There is now growing evidence that NSAID ingestion may also adversely affect small and large bowel integrity and function in man. Langman *et al* have thus shown that a significant number of patients with small bowel and colonic perforations and/or haemorrhage requiring hospitalisation are receiving NSAIDs,²⁹ and Rampton *et al* have shown that an excessive number of patients with ulcerative colitis in relapse have received analgesics in the preceding weeks.³⁰ A few doses of indomethacin (0.2–0.3 mg/kg) produced small bowel perforations in four out of 44 neonates and preterm infants requiring the drug for closure of a patent *ductus arteriosus* confirming the original observation of Nagaraj *et al*.^{31 32} Additionally it appears that NSAIDs can cause small bowel strictures and it is clear that in one of the earliest descriptions of potassium induced small bowel ulceration and strictureing, many patients were also receiving NSAIDs.^{33–36} More recent studies with $^{111}\text{indium}$ leukocytes suggest that up to 70% of long term NSAID users have evidence of small bowel inflammation which may underly the aforementioned complications.¹⁵

The intestinal barrier function is fully developed early in neonatal life and it has been suggested that its disruption plays an important part in the aetiology of various gastrointestinal disease.^{37 38} The intestinal barrier to passive diffusion is thought to be the first cell layer along with the intercellular junctions between adjacent enterocytes.³⁹ The $^{51}\text{CrEDTA}$ absorption test specifically tests the integrity of these junctions.^{40 41} This study shows that NSAIDs increase intestinal permeability to $^{51}\text{CrEDTA}$ rapidly and the effect appears to be reversible in normal subjects because many normal baseline permeability estimations were done after the studies with NSAIDs. The precise site of increase absorption of $^{51}\text{CrEDTA}$, and in particular the contribution of the gastric mucosa is however uncertain because NSAIDs frequently cause gastric damage. Two lines of evidence would, however, suggest that the stomach is not contributing significantly to the overall absorption of $^{51}\text{CrEDTA}$. First, in a previous study in rheumatoid patients on NSAIDs it was clear that increased excretion of $^{51}\text{CrEDTA}$ applied to both the 0–6 and the 6–24 hour urine collection, after oral administration.¹³ Second, this study shows that the NSAID effect on increasing intestinal permeability differs markedly from their potency to cause gastric damage. Thus, aspirin which is most frequently implicated in gastric mucosal damage only increased intestinal permeability slightly while indomethacin, which

appears to cause less damage, has a more marked effect on permeability.²⁸ The effect is systemically mediated and the increased permeability is proportional and related to drug potency to inhibit cyclooxygenase. Quantitatively the increased permeability after indomethacin is similar to that seen in patients with active Crohn's disease⁴² and in untreated patients with coeliac disease⁴³ where freeze fracture studies show structural abnormalities and widening of intercellular junctions.⁴⁴ It is of particular relevance that NSAID induced increased intestinal permeability cannot be explained by a change in the permselectivity of the tight junctions.³⁹ Thus at a neutral pH a proportion of the ⁵¹CrEDTA is ionised and bears a single negative charge.⁴⁵ This, in effect, facilitates its absorption under normal circumstances as there is an electrostatic gradient across the paracellular shunt pathway, the lumen being negatively charged in relation to the serosa.⁴⁶ NSAIDs decrease the charge across the mucosa, as assessed by measurement of potential differences,⁴⁷ and this should in effect, other factors being unchanged, decrease the absorption of ⁵¹CrEDTA. The morphological correlate of NSAID induced barrier disruption is therefore likely to reside at the level of the intercellular junction as previously suggested using other techniques.⁴⁷ The increased urine excretion of ⁵¹CrEDTA after oral administration of indomethacin is not caused by increased glomerular filtration rate as some have suggested.^{48 49} On the contrary, our data shows that indomethacin reduced glomerular filtration rate by about 10% in normal subjects. This is in accordance with other studies where less sensitive techniques were used to assess glomerular filtration rate.^{17 18 50} Theoretically it would seem clear that a two-fold increase in glomerular filtration rate would only fractionally increase recoveries of ⁵¹CrEDTA in 24 hour urines⁵¹ and as the renal handling of ⁵¹CrEDTA is similar to urea it can be estimated that glomerular filtration rate needs to be reduced to less than 30 ml/min before the 24 hour urine recoveries of ⁵¹CrEDTA would be appreciably affected.

Increased intestinal permeability due to NSAIDs precedes evidence of inflammation by some months if not by a year or two. This differs from that seen in the experimental animal where there is a latent period of 24 hours after NSAIDs, characterised by greatly reduced cyclooxygenase activities and this in turn is followed by macroscopic evidence of inflammation which probably represents a bacterial infection.⁸ The NSAID doses used therapeutically in man and in the present study are, however, many times smaller than used in animals and are likely to achieve the same levels of cyclooxygenase inhibition. Whether reduced mucosal prostaglandin pro-

duction, the concomitant metabolic diversion of arachidonic acid through the lipooxygenase pathway or even an imbalance between the products of the two pathways is responsible for the observed increased intestinal permeability is unknown. The precise mechanism(s) by which such changes cause damage to the intercellular junction is speculative and could be due to a number of factors such as reduced blood flow, mast cell degranulation, lysosomal release, etc.^{22 47} The NSAID induced damage to the intercellular junctions is, however, unlikely to be the only factor contributing to weakened mucosal resistance to microbial invasion because small intestinal inflammation is not seen in chronic alcoholics who also have increased intestinal permeability and quantitatively to a similar extent as seen following NSAIDs.²³

Naturally occurring prostaglandin E₂ have been shown to be cytoprotective for aspirin and indomethacin induced gastric erosions in man and the coadministration of prostaglandin E₂ and NSAIDs has been advocated in the hope of preventing the stomach side effects.⁵²⁻⁴ In view of the prevalence of small bowel inflammation caused by NSAIDs and the possible role of decreased mucosal prostaglandin levels in increasing intestinal permeability it was of particular interest to study whether coadministration of prostaglandin E₂ with indomethacin would be effective since if successful, this might offer a way of preventing the subsequent development of inflammation. While prostaglandin E₂ decreased the basal absorption of ⁵¹CrEDTA modestly it did not prevent the indomethacin induced increased intestinal permeability. Prostaglandin E₂ is rather unstable in acid which could have accounted for the lack of effect. The administration of ranitidine did not, however, further reduce the absorption of ⁵¹CrEDTA. This lack of effect does not exclude the possibility that NSAIDs increase intestinal permeability through their inhibitory action on cyclooxygenase as the dose of prostaglandin E₂ was low which may have resulted in inadequate levels in the more distal parts of the intestine. Larger doses that afford substantial protection in the stomach are, however, associated with nausea and diarrhoea. The recently developed potent and stable prostaglandin analogues with less gastrointestinal side effects may be more suitable for the prevention of NSAID induced increased intestinal permeability.⁵⁵

The authors are grateful to Dr Norman Veall and the staff of the Radioisotopes Division for their help with the supply and measurements of the ⁵¹CrEDTA.

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