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Intestinal permeability, non-steroidal anti-inflammatory drug enteropathy and inflammatory bowel disease: an overview

INGVAR BJARNASON AND TIMOTHY J PETERS

'What we call progress is the exchange of one nuisance for another nuisance'

Henry Mavlock Ellis

Historical background

There is recent renewed interest in the role of the intestine in the pathogenesis of the various arthritides[1-7]. In general, it is postulated that an intestinal microbial constituent or product is absorbed by the intestinal mucosa eliciting an immunological response and tissue damage by simple or induced molecular mimicry[8-10]. The difference between the two mechanisms can best be shown by considering the proposed pathogenesis of ankylosing spondylitis which has a strong association (96% in Europe) with HLA-B27. Proponents of simple molecular mimicry would suggest that the frequent finding of certain Klebsiella species in the stools of patients with ankylosing spondylitis implies that a Klebsiella macromolecule may have an amino acid sequence homology with a region of the HLA-B27 molecule itself so that an immunological response towards the Klebsiella antigen would cross react with the HLA B27 protein[6]. Such a sequence has indeed been found for 10 consecutive amino acid residues of the enzyme nitrogen reductase, which is found in 10% of Klebsiella species, and in the HLA-B27 molecule.[10 11] The induced molecular mimicry theory states that a putative macromolecule binds directly to the HLA-B27 molecule so that it is no longer recognised as 'self'. Both theories are controversial but are susceptible to further investigation. With regard to the intestine, it is important to realise that if the simple molecular mimicry theory holds true there need not be a severe disruption of the intestinal barrier function as the antigen would only have to gain access to the lamina propria, whereas if the latter theory is operational there would have to be profound loss of intestinal integrity so as to allow a significant antigenaemia.

Regardless of the precise cascade of events it is clear that the assocation between intestinal defects and the various arthritides ranges from almost certainty with Salmonella, Shigella, Yersinia, and Campylobacter infections, as well as the less specific intestinal bacterial overgrowth syndrome which may follow intestinal bypass surgery[12-16] to the speculative with rheumatoid arthritis.[17 18] The idea of infection and rheumatoid arthritis dates back to the last century and culminated in the theory of focal sepsis which in turn was translated into the common therapeutic practice of total tooth extraction, removal of tonsils and adenoids, and even colectomy in an attempt to cure the disease.[5] After their failure, the idea was resurrected in Scandinavia and, after some sound scientific work, led to the use of sulphasalazine in rheumatoid arthritis and inflammatory bowel disease.[19 20] The idea has by no means fallen into obscurity and Ebringer has recently suggested a pathogenic role for *Proteus mirabilis* in rheumatoid arthritis after showing high antibody titres of this common pathogen in patients with rheumatoid arthritis.[6]

A gastroenterological approach to the problem was initiated by us five years ago and the results show that most of the intestinal abnormalities encountered in patients with rheumatoid arthritis are the result of the use of non-steroidal anti-inflammatory drugs (NSAID). Moreover, it is apparent that the small intestine is an important site of NSAID-related gastrointestinal toxicity, contributing significantly to the morbidity of patients with rheumatoid arthritis.[21-25]

Intestinal permeability

The small intestine has the paradoxical dual functions of being a digestive/absorptive organ and acting as a barrier to the permeation of toxic compounds and macromolecules.[26 27] It only became feasible to access the intestinal barrier function non-invasively in man after the pioneering work of Menzies in the 70s.[28] Essentially it is suggested that the transfer of hydrophilic macromolecules (Mr >300 dalton) is limited by the small size of aqueous pores in the otherwise lipophilic brush border membrane and by the integrity

of the intercellular junctions.[29] The intercellular junctions appear to be particularly susceptible to a variety of noxious agents and may be one of the first organelles to suffer when the energy production of the enterocyte is compromised. This would result in disruption of intercellular integrity allowing increased permeation of macromolecules into the mucosa. The regulatory mechanisms governing intercellular structural and functional integrity are, however, largely unknown.[30] Increased intestinal permeability, moreover, is not automatically synonomous with antigen permeation as other host defence mechanisms interact to limit the permeation and the biological effects of the macromolecules.

During initial evaluation of ^{51}Cr EDTA as a permeability marker it was clear that patients with rheumatoid arthritis had markedly increased intestinal permeability and often similar to that seen in coeliac and inflammatory bowel disease.[21 31 32] Patients untreated by NSAIDs, had entirely normal intestinal permeability despite active disease. Further studies in patients with osteoarthritis and healthy volunteers have clearly established that NSAIDs do indeed increase intestinal permeability.[21 22] The increased intestinal permeability relates to the potency of the drug to inhibit cyclooxygenase and, as is evident from studies of fractional urine collections, damage occurs throughout the intestine rather than being localised to the proximal small intestine. This has been shown, for example, for indomethacin administered as a suppository.[22] The situation is more complex however, because the effect of most NSAIDs on the gut can be envisaged as a summation of three events.[33] Initially, during drug absorption there is a high local concentration of NSAID in the proximal small bowel where it exerts its full metabolic effects. After absorption the drug is distributed widely and diluted so that the systemic effect is only a fraction of what occurs locally during absorption. Third, most NSAIDs are secreted in bile to a significant extent which may further expose the small intestine to the drug. Consideration of the above and the fact that NSAIDs frequently cause inflammation of the small intestine in the experimental animal and humans rather than damage to the colon,[34] has led us to concentrate our studies on the small intestinal effect (0–5 hour urines) of NSAIDs on intestinal permeability.

If, as suggested, NSAIDs damage the intestine by inhibiting cyclooxygenase thereby reducing mucosal prostaglandin production and diverting arachidonic acid metabolism into the lipooxygenase pathway, this will lead to increased production of proinflammatory leukotrines. This hypothesis had been assessed indirectly in volunteers by the coadministration of prostaglandins with NSAIDs. Misopostol a stabile prostaglandin E_1 analogue had no effect on Naproxen induced increased intestinal permeability when given independently.[35] When given at relatively high doses half an hour before indomethacin, however, misoprostol had a significant protective effect.[36] Moreover a small dose of rioprostol given at the same time as indomethacin has a maximal protective action [37] suggesting that it is the initial damage during absorption of the NSAID that is the most important of the three phases in increasing small intestinal permeability. As we believe that it is this initial and immediate effect of NSAID to increase small intestinal permeability which is the prerequisite for the subsequent development of small intestinal inflammation by exposing the mucosa to luminal substances and perhaps, as in the experimental animal, paving the way for a bacterial invasion, further studies should concentrate on the means by which NSAID-induced increased intestinal permeability can be prevented.

There are a number of ways of examining the mechanism by which NSAIDs increase intestinal permeability. Most NSAIDs have a carboxylic acid residue which, by virtue of a low pk, may be locally irritating. Non-steroidal anti-inflammatory drugs may increase lysosomal fragility by the generation of oxygen derived free radicals, potentiated by vasoconstriction. Thus the simultaneous administration of free radical scavengers may be beneficial. It is suggested that NSAIDs damage the small intestine of the experimental animal by inhibiting steps in the anaerobic glycolytic pathway and the tricarboxylic acid cycle. This results in a reduced synthesis of ATP thereby impairing the survival of the injured cell.[38] The administration of glucose and citrate, the metabolic precursors for glycolysis and the TCA cycle respectively, protect against damage medicated by indomethacin in the experimental animal.[38] Preliminary results suggest a similar reduction in the indomethacin induced effects on intestinal permeability in man. Agents that selectively inhibit lipooxygenase and thromboxane synthase (dazmegril) could provide a means of exploring the mechanisms of NSAID toxicity to the small intestine. Finally the effects of pro-NSAIDs would be of particular interest in distinguishing between the importance of local *versus* systemic toxicity since these drugs are only activated in the liver after absorption and, at least with nabumatone (Relifex), there is no biliary excretion of the active drug.

Whatever the final mechanism underlying the increased intestinal permeability due to NSAIDS, the objectives of the above studies are two-fold. First, they could establish, in longterm studies, the pathogenic importance of altered intestinal permeability and, second, they offer the prospect of reducing the frequency and severity of the associated complication of NSAID enteropathy.

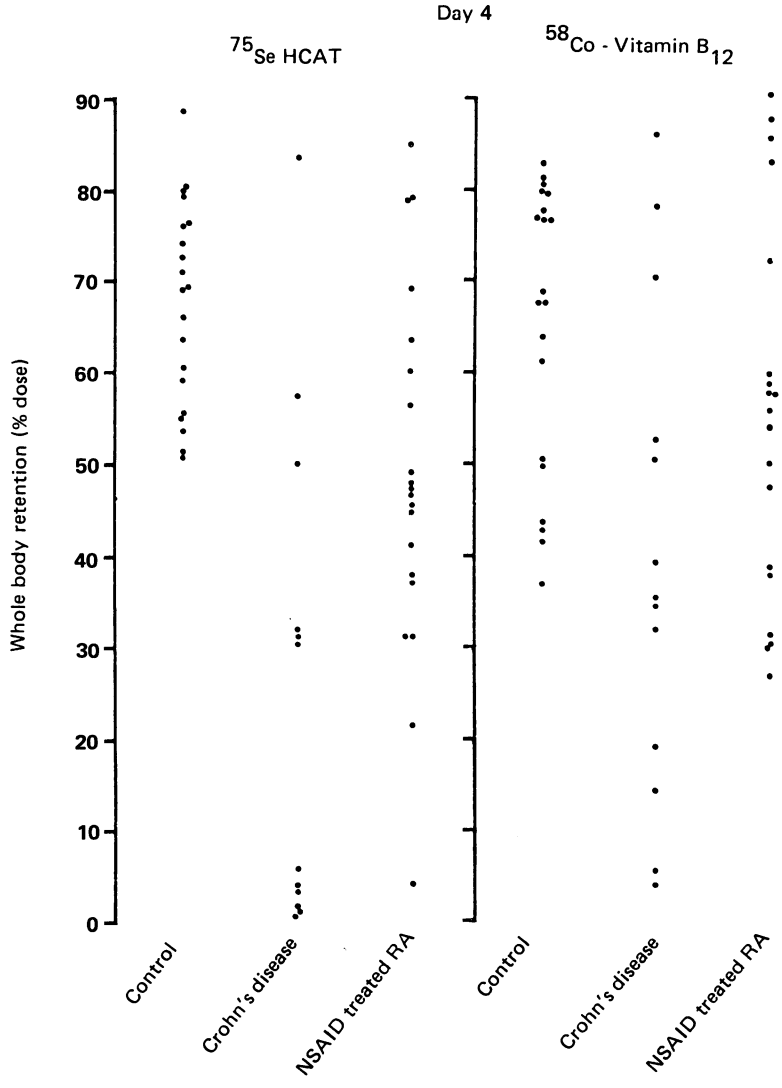

Fig 1 *Whole body retention of ^{75}SeHCAT and ^{58}CovitB$_{12}$ + intrinsic factor four days after oral administration.* Reprinted with permission from Non-steroidal anti-inflammatory drug induced small intestinal inflammation in humans by Bjarnason *et al*, *Gastroenterology* 1987; **93:** 480–9. Copyright 1987 by the American Gastroenterological Association.

NSAID enteropathy

Because permeability changes with NSAIDs are quantitatively similar to those found in inflammatory bowel disease, evidence of intestinal inflammation was specifically sought with ^{111}Indium labelled leucocytes.[21 23 31 32] The technique has been extensively validated for the localisation of occult infections and segmental involvement in inflammatory bowel disease. There is a good correlation between scintigraphic and radiological location of inflammatory bowel disease and between ^{111}Indium faecal excretion and clinical correlates for quantitation of disease activity. Depending on whether intestinal inflammation was judged by abdominal scintigrams or by the four day faecal excretion of ^{111}Indium, 45% and 70%, respectively, of patients on longterm NSAIDs have evidence of intestinal inflammation.[23] The inflammation is only consistently evident after more than six months of NSAID ingestion. No particular NSAID has been selectively implicated in the development of the inflammation although the

assessment noted only the drug that the patients were taking at the time of study: the majority of patients received a number of different NSAIDs at different times. Nevertheless, no correlation has been found between the activity of rheumatoid arthritis and the faecal excretion of ^{111}Indium and as with the permeability tests, patients with rheumatoid arthritis who had not received NSAIDs had entirely normally ^{111}In studies. Patients with osteoarthritis treated with NSAIDs also had small bowel inflammation confirming that the inflammation was indeed caused by the NSAIDs. Interestingly, when patients stopped taking NSAIDs after years of ingestion, it took up to 16 months for the intestinal inflammation to resolve. It might be suggested that the granulocytes were accumulating in the intestine as a non-specific consequence of the increased intestinal permeability, but this ignores the complexities and specificity of neutrophil migration and activation.[30] Nevertheless histological correlates of the inflammation is lacking. Mielants *et al*[7] found no terminal ileal inflammation in biopsies from 20 patients with rheumatoid arthritis on NSAIDs and we found only minor changes in one of nine patients on NSAIDs undergoing jejunal biopsies.[23] Neither observation is unexpected as the inflammation may be predominantly lower jejunum and upper ileum as in the experimental animal and the inflammation is relatively low grade and diffuse. The importance of NSAID enteropathy lies in the associated clinical complications rather than in any histological abnormalities.

Blood loss

Thirty two patients on NSAIDs underwent simultaneous study with ^{111}In leucocytes and ^{99m}Tc red cells followed by abdominal scintigraphs to locate the two isotopes.[24,25] In 19 patients there was identical intestinal location of the two isotopes, in four there were discrepancies and nine were normal by both techniques. Thus, the small intestinal inflammation is associated with significant blood loss. When simultaneous studies were made in 29 patients on NSAIDs quantifying both the faecal ^{111}In activity and the ^{51}Chromium red cell intestinal blood loss a significant correlation was found between the two ($r:0{\cdot}59$, $p<0{\cdot}01$), further supporting the idea that NSAID enteropathy is associated with intestinal bleeding.

The clinical importance of a chronic daily blood loss of 1–8 ml depends on a variety of factors, but essentially revolves around iron homeostasis. Iron homeostasis is assured by an adequate intake of a nutritious diet, the availability of iron for absorption, the regulation of the intestinal iron transport and, of course, the basal iron loss. In the context of patients with rheumatoid athritis it is clear that many of the above factors may be impaired so as to render them borderline iron deficient. Thus cachexia associated with active disease as well as dyspepsia due to NSAIDs may limit food intake. Hypochlorhydria as a result of antacids, pernicious anaemia or chronic gastritis may reduce the availability of iron for absorption. The activity of the intestinal iron transport system is impaired in relation to their iron stores. It is under these circumstances that mild chronic blood loss from the gut has its greatest clinical impact in depleting existing iron stores and rendering the patients iron deficient. The precise definition of an iron deficient anaemia in the rheumatoid patient is, however, difficult as it is often superimposed on the anaemia of chronic disease which is of course associated with an erythroid precursor defect in assimilating available marrow iron. Nevertheless many rheumatologists empirically treat patients with haemoglobin levels

Fig 2 *Two diaphragmatic strictures caused by NSAIDs cut to show the thickness. (2–3 mm).*
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below 10 g/dl with iron, with improvement, but not normalisation of haemoglobin levels.

Protein loss

Nine patients on NSAIDs underwent a simultaneous study with ^{111}In leucocytes and a study of intestinal protein loss using $^{51}CrCl_3$. All six patients with NSAID enteropathy had a protein losing enteropathy but the number of patients was too small to assess reliably whether there was a significant correlation between the two variables. The importance of chronic protein loss has to be viewed in the context of whole body protein turnover, but may explain the hypoalbuminaemia of some patients with rheumatoid arthritis. Considering the number of patients on long term treatment with NSAIDs this may be one of the most frequent causes of a protein losing enteropathy world wide.

Ileal dysfunction

Ileal function was assessed by whole body retention of orally administered [^{75}Se] labelled-25-homocholic acid (^{75}SeHCAT) and ^{58}Co labelled cyanobalamin (^{58}Co vitB_{12}). The purpose of the study was not only to assess ileal function in 20 patients on NSAIDs but also to compare the sensitivity of the two markers in 13 patients with ileal Crohn's disease.[23] The results showed that 13 of 20 patients on NSAIDs had ^{75}Se HCAT malabsorption of whom four only had borderline reduced absorption of ^{58}Co vitB_{12}. In the Crohn's patients ^{75}Se HCAT was found to be a much more sensitive indicator of ileal function than ^{58}Co vitB_{12}. Furthermore ^{58}Co vitB_{12} was such a poor indicator of ileal function as to render the test quite useless for screening purposes (Fig. 1). Despite the considerable bile acid malabsorption in both Crohn's disease and NSAID enteropathy none of the patients had diarrhoea at the time of study.

Small intestinal strictures

There are anecdotal case reports of small intestinal ulcers and strictures in patients on NSAIDs.[40,41] Medhock *et al* described three patients where there is little doubt that NSAIDs caused small intestinal ulcers.[42] We reviewed all small intestinal resection specimens at Northwick Park Hospital over a 16 year period and found what we believe are unique small intestinal strictures caused by NSAIDs (Fig. 2) that represent a new nosological entity.[43] The strictures were ileal, 3–70 in number, concentric, diaphragm septa like 2–4 mm in thickness which narrowed the intestinal lumen to a pinhole. These are notoriously difficult to diagnose and can be easily missed at laparotomy unless specifically sought. Differentiation between an intestinal diaphragm caused by NSAIDs and the congenital variety can usually be made by the history, location and the number of strictures but the histopathology may be strikingly similar.

Treatment of NSAID enteropathy

Therapy is often based on the understanding of the disease process but more often it is empirical. As, NSAID enteropathy has so many similarities with Crohn's disease of the small intestine, however, we have attempted treatment with sulphasalazine. As patients with active agressive rheumatoid arthritis benefit from sulphasalazine the initial study involved only patients requiring a second line agent. Forty patients were studied before and after sulphasalazine and 20 before and after other second line drugs – for example, gold, penicillamine, chloroquine, while maintaining an unchanged NSAID intake. Sulphasalazine reduced significantly the faecal ^{111}In excretion while the other second line drugs did not (data submitted). Both groups of patients benefitted similary with regard to reduced joint inflammation. There was, however, no significant correlation between the beneficial response of sulphasalazine on the joints and the intestine suggesting the NSAID enteropathy does not have a detrimental effect on the joints as previously suggested. Preliminary studies assessing intestinal blood loss, as well as inflammation, before and after sulphasalazine suggest that reduced intestinal inflammation is matched by reduced intestinal blood loss.

The implication of these studies will depend on our perception of the problem. In mild cases of rheumatoid arthritis where the patient needs only simple and infrequent analgesics nothing needs to be done. In contrast the badly controlled patients who frequently develop iron deficiency without 'apparent' cause needs careful consideration. Clearly sulphasalazine might be a suitable first choice of drug under these circumstances, especially as iron supplements are so badly tolerated by many of these patients. The next question is what to do about the majority of patients with rheumatoid arthritis. In view of the high prevalence of NSAID related gastrointestinal damage we would propose to use sulphasalazine at a much earlier stage in rheumatoid arthritis than is currently practised. This may reduce the severity of NSAID enteropathy as well as reducing dependence on these drugs and, more speculatively offers the hope of altering the natural history of rheumatoid arthritis.

NSAID enteropathy and Crohn's disease

It is strikingly evident that there are close similarities

between established NSAID enteropathy and small bowel Crohn's disease with regards to clinical and functional features as well as response to similar therapeutic manoeuvres. Moreover NSAIDs may cause a relapse of quiescent inflammatory bowel disease suggesting an interesting interaction between increased intestinal permeability causing increased permeation of luminal substances and activity of the inflammatory process. It is also of interest to consider the parallel increase in the incidence of Crohn's disease with the increased consumption of over the counter NSAID preparations in Western societies.

Detailed study of the mechanism of preserving the structural and functional integrity of the intestinal barrier function with special reference to the role of ecosanoid synthesis and metabolism in NSAID enteropathy are clearly indicated an may have implications for elucidation of the processes involved in the development of human inflammatory bowel disease.

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Sect Gastroenterology MRC Clinical Research Centre,
Harrow,
Middlesex HA1 3UJ,
United Kingdom

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