Non-steroidal antiinflammatory drugs and the intestine

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Only in the past two decades, NSAID enteropathy became fully appreciated as a potentially important clinical entity. Its incidence is much less common than NSAIDs associated upper GI lesions but its exact prevalence remains unknown. The most important reasons are that intestinal lesions are difficult to explore requiring invasive techniques and manifest themself mostly only by complications.

A. Animal model

The severe inflammation in *jejunum and ileum* in rats after the ingestion of indomethacine has been well documented (1-3). Enterohepatic recirculation of NSAID, endoluminal factors from bacterial, alimentary or biliary origin and the production of free oxygen radicals seem implicated in the etiopathogenesis of this inflammation.Enterohepatic recirculation is probably the most critical factor since bile duct ligation or administration of NSAIDs without enterohepatic recirculation (e.a. nitrofenac) prevent the development of the inflammation (1,4,5). A role for enteric bacteriae has been suggested, based on the large increase in bacterial numbers in the small intestine after NSAID administration, the ability of antibiotics to attenuate the inflammation and the reduced severity of damage in germ-free rats (6-8).

A role of free oxygen radicals is supported by the beneficial effect of scavengers.

Finally, intestinal inflammation is attenuated by the administration of NO-NSAIDs. NO is a strong vasodilator neutralizing the ischemic effects of NSAIDs and suppressing the adherence of neutrophils to the vascular endothelium (5,9,10).

NSAIDs also exacerbate preexisting *colonic* ulceration and inflammation in laboratory animal models (11). Unlike the case for small intestinal injury, enterohepatic circulation does not play an essential role. Inhibition of colonic mucosal prostaglandins seems to be the most likely mechanism of injury and not the accompanying enhanced leukotriene production.

B. Human effects

Human enteropathy can be divided in asymptomatic lesions with questionable clinical importance and macroscopic symptomatic lesions.

1. *Subclinical alterations*

The asymptomatic alterations include an increase in permeability, an accumulation of leucocytes in areas of inflammation and the presence of asymptomatic lesions discovered during enteroscopy or autopsy.

- Intestinal permeability.

An increase in paracellular permeability, measured by the use of Cr51EDTA, has been observed after the ingestion of NSAIDs in normal volunteers and in patients with rheumatoid arthritis, osteoarthrits and ankylosing spondylitis (12-16). This effect is partially reversible by the administration of prostaglandins and can be prevented by metronidazole.

We performed a prospective study about the intestinal permeability in patients with spondyloarthropathy (SpA) treated or not with NSAIDs and compared these results with those observed in patients suffering from osteoarthritis (17).

In SpA patients NSAIDs-free, we found a significant increase in the urinary recovery of $Cr^{51}EDTA$ 1 to 6 hours after the ingestion as compared to patients with osteoarthritis. These findings support the previously reported small intestinal inflammation in SpA (18). In patients treated with NSAIDs, we found a significant increase in the late urinary recovery of $Cr^{51}EDTA$ (6-24 hours) in all groups of patients. These results support the findings of Jenkins *et al.* (13) suggesting that NSAIDs increase predominantly colonic permeability but contrast with those of Bjarnasson reporting principally an increase in small intestinal permeability (5).

- Intestinal inflammation

The presence of intestinal inflammation has been suggested by scintigraphic studies. A late accumulation of 111 Indium in the right iliac fossa has been observed in about half of the patients on NSAIDs. This accumulation seems to occur only several months after the

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initiation of the treatment and to persist for more than 18 months after discontinuation of the drugs (12). The exact interpretation of this abnormality remains controversial since Segal *et al.* were not able to relate this inflammation with the intake of NSAIDs (19).

– Endoscopy and autopsy

The presence of an asymptomatic enteropathy has been confirmed by an enteroscopic study in patients with rheumatoid arthritis treated with NSAIDs. Mucosal red spots or erosions in jejunum have been observed in about half of the patients (20). In contrast, no macroscopic or miscroscopic lesions related to the use of NSAIDs were demonstrated in terminal ileum of patients with spondyloarthropathy (15,21). The reported inflammation in about 60% of these patients was only related to the articular disease and not to the intake of the drugs.

In a prospective autoptic study, nonspecific small intestinal ulcers were described in 8.4% of patients on NSAIDs and in 0.6% of the non-users (22). These ulcerations varied from single ulcers to confluent and stenosing ulcerations.

The etiopathogenesis of the enteropathy suggested by Bjarnasson starts with a dissociation of mitochondrial oxidative phosphorylation inducing an ATP depletion in the enterocytes. This loss in energy results in a disruption of the epithelial junctions and an increase in mucosal permeability. Simultaneously, a leakage of calcium into the cytosol induces the generation of oxygen free radicals and compromises the cellular function.

The increased permeability permits the penetration of luminal agents, induces a chemoattractive effect on neutrophils, inflammation and mucosal damage.

2. *De novo lesions*

Isolated ulcerations, eventually complicated by bleeding or perforation have been demonstrated in several studies (23). The exact mechanism remains unknown but a direct toxic effect seems most probable because these lesions are frequently observed after the use of slow-release forms of NSAIDs and with the use of suppositories.

Best known but very rare are *diaphragm-like structures* in small intestine and colon associated with submucosal fibrosis. These diaphragms are formed by concentric, symmetric, thin septa with a small central opening. They are usally not visible on conventional radiology because they look like normal plicae circulares. On laparatomy, inflation of air is necessary to demonstrate these areas of retraction because they are not associated with distortions of the intestinal wall (24).

Various forms of *colitis* have been described after the use of NSAIDs varying form aspecific colitis, to eosinophilic colitis, pseudomembranous colitis, collagenous colitis and even ischemic colitis (25). This colitis may start several days or years after the start of the treatment and seems associated with the inhibition of prostaglandins necessary to maintain the integrity of the mucosa and its repair. A spontaneous resolution is normally observed after the interruption of the treatment (4).

Aspirine and some other NSAIDs *reduce the intestinal* absorption of glucose, sodium and water (26,27). Chronic diarrea with steatorrhea has been reported after the intake of mefenonic acid (28). A reduced absorption of Vit B12 and bile acids has been reported in patients treated with NSAIDs (29).

C. Effects on pre-existing diseases

NSAIDs may be responsible for complications in *diverticular disease* as suggested by a case control study (30) and supported by a prospective study (31). Several cases of reactivation of *inflammatory bowel disease* (IBD) attributable to NSAIDs have been described (25,32,33). A higher risk for emergency admission to hospital was described in colitis patients. These effects seem linked to the inhibition of the enzyme COX2 and the derived production of prostaglandins. In a recent study, Singer *et al.* (34) demonstrated that COX2 was undetectable in the normal mucosa of ileum and colon, but that its expression was induced in apical epithelial cells of inflamed foci in IBD. Animal models suggest that PGs produced through COX-2 promote wound healing in gastrointestinal mucosal injury. This raises the possibility that the expression of COX-2 in IBD is a protective response and the future use of selective COX2 inhibitors may have a deleterious effect on IBD. They would not be expected to damage the normal gut because it does not express COX-2.

D. Therapeutic effects

In general, NSAIDs remain the cornerstone of the treatment of spondyloarthropathies. However in these studies ,data about the effect of the drugs on the bowel are rare. Since a clear positive relationship has been demonstrated between evolutions of gut inflammation and articular disease, their effects seem not deleterious (21). No data are available about the effect of NSAIDs on intestinal symptoms of patients with IBD associated arthropathy. Prospective multicentric studies are required to evaluate the effects of different treatment modalities.

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