Strictures, diaphragms, erosions or ulcerations of ischemic type in the colon should always prompt consideration of nonsteroidal anti-inflammatory drug-induced lesions

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AIM: To investigate whether NSAIDs/ASA lesions in the colon can histologically be diagnosed on the basis of ischemic necrosis similar to biopsy-based diagnosis of NSAIDs/ASA-induced erosions and ulcers of the stomach.

METHODS: In the period between 1997 and 2002, we investigated biopsy materials obtained from 611 patients (415 women, 196 men, average age 60.5 years) with endoscopic focal erosions, ulcerations, strictures or diaphragms in the colon. In the biopsies obtained from these lesions, we always established the suspected diagnosis of NSAID-induced lesions whenever necroses of the ischemic type were found. Together with the histological report, we enclosed a questionnaire to investigate the use of medication. The data provided by the questionnaire were then correlated with the endoscopic findings, the location, number and nature of the lesions, and the histological findings.

RESULTS: At the time of their colonoscopy, 86.1% of the patients had indeed been taking NSAID/ASA medication for years (43.9%) or months (29.5%). The most common indication for the use of these drugs was pain (64.3%), and the most common indication for colonoscopy was bleeding (55.5%). Endoscopic inspection revealed multiple erosions and/or ulcers in 60.6%, strictures in 15.8%, and diaphragms in 3.0% of the patients. The lesions were located mainly in the right colon including the transverse colon (79.9%). A separate analysis of age and sex distribution, endoscopic and histological findings for NSAIDs alone, ASA alone, combined NSAID/ASA, and for patients denying the use of such drugs, revealed no significant differences among the groups.

CONCLUSION: This uncontrolled retrospective study based on the histological finding of an ischemic necrosis shows that the histologically suspected diagnosis of NSAID-induced lesions in the colon is often correct. The true diagnostic validity of this finding and the differentiation from ischemic colitis should, however, be investigated in a prospective controlled study.

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Key words: Erosion; Ulceration; Stricture; Diaphragm; Ischemic necrose; NSAIDs; ASA

INTRODUCTION: The first publications of NSAID-induced strictures in the small bowel[1,2] and colon[3,4] were followed by a number of reports that the intake of NSAIDs leads not only to such pathological changes as chemically-induced reactive gastritis, subepithelial bleeding, erosions and ulcerations complicated by bleeding or perforation in the stomach and duodenum[5,6], but also to erosions, ulcerations, perforations, bleeding[7-10,12,17], strictures and symptomatic diverticular disease[8,9] in the small and large bowel[5,10]. In animal experiments, it has been shown that as little as a single dose of NSAIDs can result in a high incidence of mortality after 3 d due to intestinal lesions and perforations[10,11].

With regard to the incidence of NSAID-induced lesions in the ileum and colon, the literature contains no reports on data obtained from controlled prospective endoscopic or endoscopy/biopsy studies. From the large Arthritis, Rheumatism, and Ageing Medical Information System databank of arthritic patients, however, it can be seen that 32% of gastrointestinal (GI) hospitalizations in osteoarthritis patients, and 13% of GI hospitalizations of patients with rheumatoid arthritis are due to lower GI diagnosis. In addition, studies of patients with spondyloarthropathy receiving conventional NSAID treatment over the long term have shown that 30-70% of these patients developed a macroscopic or microscopic ileitis, and, with varying frequency, inflammation of the cecum or colon[12-20].

In a post hoc analysis of 8,076 patients with rheumatoid arthritis who were treated with a non-selective NSAID (naproxen) or coxib (rofecoxib), serious lower intestinal events (bleeding, perforation, obstruction, ulceration, and...
diverticulitis) were found. The rate of events per 100 patient years was 0.41 for rofecoxib and 0.89 for naproxen. Serious lower GI events accounted for 39.4% of all serious GI events among patients taking naproxen, and 42% among those taking rofecoxib\cite{25}.

NSAIDs preparations not only inhibit prostaglandin synthesis via COX inhibition\cite{26}, but also uncouple mitochondrial oxidative phosphorylation\cite{27}. These substances also cause local topical toxicity\cite{28}, since they are lipid-soluble weak acids that can lead to interaction with surface membrane phospholipids and thus disruption of the gastric epithelial cell barrier and to back diffusion of acid into the mucosa\cite{29,30}.

Mucosal injuries in the gastrointestinal tract (GIT) are also a consequence of NSAID-induced liberation of vasoc-onstricting leukotrienes\cite{31,32}, free radicals, platelet thrombi and proteases\cite{33,34,36}. Other publications have demonstrated a connection between NSAID-induced microcirculatory disorders and the adhesion of neutrophil granulocytes to vascular endothelium. In addition, liberation of TNF-α is triggered, which is responsible for the liberation of the intracellular adhesion molecule-1 at the vessel walls, and which can lead to local microcirculatory disorders due to vascular spasms\cite{35,37}. All these synergistic interactions\cite{38,39}, particularly the microcirculatory disorders caused by spasms of the tiny blood vessels, can give rise to ischemic erosions and ulcerations in the GIT\cite{40-44} and to diaphragm-like strictures\cite{46,48-51}. Since these lesions may be the cause of blood in the stools or a positive hemoccult test, and the bleeding may lead to chronic hemorrhagic anemia\cite{45,54}, the indication for colonoscopy is now being established more frequently in this group of patients. Since colonoscopic biopsies are always taken from macroscopically identifiable lesions, the question arises as to whether the pathologist can establish a suspected diagnosis of NSAID-induced lesions in the biopsy material, and how reliable this suspected diagnosis is. Having already shown that NSAID-induced erosions\cite{52} and ulcerations\cite{56} of the gastric mucosa can often be identified on the basis of necrosis of the ischemic type, we have now examined the question whether this type of necrosis might not also be a suitable diagnostic criterion for NSAID-induced lesions in the colon.

MATERIALS AND METHODS

From 1997 to 2002, we investigated biopsy materials obtained from 611 patients (415 women, 196 men, average age 60.5 years) with focal erosions, ulcerations, strictures or diaphragms at endoscopy. In the biopsies obtained from these lesions, we always established the suspected diagnosis of NSAID-induced lesions in the biopsy material, and how reliable this suspected diagnosis is. Having already shown that NSAID-induced erosions\cite{52} and ulcerations\cite{56} of the gastric mucosa can often be identified on the basis of necrosis of the ischemic type, we have now examined the question whether this type of necrosis might not also be a suitable diagnostic criterion for NSAID-induced lesions in the colon.

RESULTS

An analysis of the information provided on NSAID/ASA ingestion by the 501 patients with a histologically suspected diagnosis of NSAID/ASA-induced lesion in the colon is presented in Table 2 and shows that 86.1% of those patients actually were on NSAID/ASA medication at the time of their colonoscopy. In most cases, NSAIDs had been used for a period of years or months (Table 3). The most common indication for the use of these drugs was pain (Table 4). The symptoms that had led to an indication for colonoscopy are shown in Table 5. Lumping together the symptoms melena and anemia, and the positive occult blood test, it can be seen that bleeding complications occur in 55.5% of the cases, and are the most common indication for colonoscopy.

The most commonly cited medication (70.5%) was diclofenac (Table 6). In 60.6% of the cases, endoscopy revealed multiple lesions (erosions or ulcers), strictures (15.8%), while diaphragm-like formations (3.0%) were relatively rare. The distribution of the location of these
lesions identifies the right colon, in particular Bauhin’s valve, as the most frequently affected site (Table 7).

An analysis of the frequency of the various lesions in terms of solitary or multiple lesions showed that multiple lesions were most commonly ulcers or ulcers in combination with erosions, while solitary lesions were mostly focal erosions. Strictures or diaphragms were also frequently associated with multiple lesions (Table 8).

A separate analysis of patient’s age and sex distribution and endoscopic findings, after dividing cases into those with NSAID use alone, ASA use alone, combined use of NSAID and ASA, and cases denying NSAID/ASA intake, are shown in Table 9. A similar analysis of the histological findings is shown in Table 10. These two analyses revealed no statistically significant differences among the four groups of patients.

**DISCUSSION**

Our analysis showed that the histologically established diagnosis of suspected NSAID/ASA-induced lesion of the colonic mucosa is probably correct in a high percentage of cases (86.1%), and focal lesions were found, mainly in the right colon, such as Bauhin’s valve, cecum and ascending colon. However, since our study was an uncontrolled retrospective study based on histological findings, the results must be considered preliminary, and needs to be checked in prospective studies.

The topographic clustering of the lesions at Bauhin’s valve, in the cecum and ascending colon prompts the hypothesis that the lesions are not very likely caused by a

| Table 2 | Answers to the questionnaire in Table 1 |
|---------|----------------------------------------|
|         | n | %  |
| NSAID   | 326 | 58.3 |
| ASA     | 122 | 20.0 |
| NSAID/ASA | 48 | 7.8  |

| Table 3 | Duration of ingestion of NSAID/ASA (%) |
|---------|----------------------------------------|
|         | D | 4.6 |
|          | Wk | 13.9 |
|          | Mo | 21.5 |
|          | Yr | 43.9 |
|          | No information | 16.1 |

| Table 4 | Indication for use of NSAID/ASA (%) |
|---------|-------------------------------------|
| Pain    | 64.3 |
| Polyarthritis | 12.3 |
| Coronary heart disease | 10.2 |
| Peripheral occlusive arterial disease | 7.9 |
| Others | 5.7 |

| Table 5 | Indications for colonoscopy (%) |
|---------|---------------------------------|
| Melena  | 23.9 |
| Positive occult blood test | 11.0 |
| Anemia  | 21.6 |
| Diarrhea | 19.4 |
| Abdominal pain | 17.7 |
| Weight loss | 1.9 |
| Ileus or subileus | 1.1 |
| Others | 1.1 |

| Table 6 | Frequency distribution of used NSAID preparations (%) |
|---------|------------------------------------------------------|
| Diclofenac | 70.5 |
| Ibuprofen | 7.3 |
| Piroxicam | 1.4 |
| Ketoprofen | 0.4 |
| Phenylbutazone | 0.2 |
| Combinations | 17.6 |

| Table 7 | Localization of the lesions (%) |
|---------|---------------------------------|
| Ileum | 4.5 |
| Bauhin’s valve | 21.3 |
| Cecum | 14.8 |
| Ascending colon | 19.1 |
| Right flexure | 7.0 |
| Transverse colon | 15.7 |
| Left flexure | 2.8 |
| Descending colon | 6.7 |
| Sigmoid colon | 5.3 |
| Rectum | 2.8 |

| Table 8 | Frequency of lesion type (solitary and multiple lesions) |
|---------|----------------------------------------------------------|
| Erosions | 63.3 | 21.3 |
| Ulcers | 21.7 | 56.4 |
| Erosions+ulcers | 0 | 12.2 |
| Regenerative mucosa | 15.0 | 10.1 |
| Strictures | 11.1 | 18.8 |
| Diaphragms | 1.0 | 4.4 |

| Table 9 | Age and sex distribution, location of lesions in right colon, and histological findings in the four groups of patients |
|---------|---------------------------------------------------------------|
|          | n | F:M | Age (yr) | Location right colon | Endoscopic solitary lesion | Endoscopic multiple lesions | Endoscopic stricture | Endoscopic diaphragm |
| NSAID    | 58.3 | 2.4:1 | 28:98 | n = 131 | n = 225 | n = 55 | n = 13 |
| ASA      | 20% | 1.6:1 | 23:90 | n = 61 | n = 61 | n = 15 | n = 1 |
| NSAID+ASA | 7.8% | 4.3:1 | 47:89 | n = 15 | n = 33 | n = 12 | n = 1 |
| NoNSAID/ASA | 13.9% | 1.4:1 | 19:90 | n = 58 | n = 27 | n = 7 | n = 1 |
generalized, but by a topical local injurious effect of the
NSAID/ASA preparations. This hypothesis is supported
by the fact that these lesions were, in many cases, associated
with the use of retard preparations, and that in particular
the “bottleneck” at Bauhin's valve was involved. In those
patients using non-retard preparations, it might be interesting
to establish whether diarrhea associated with rapid transit
of the medication into the colon was present. This point
would have to be clarified in a prospective study, since we
did not request information about a temporal relationship
to diarrhea and the use of the medication. In support of a
topical mucosa-injuring effect of NSAID/ASA, there are
also numerous case reports on the use of retard preparations
and on the preferential sites of the lesions in the right
colon[42,44,50,53].

Also surprising are the results of our comparative analysis
of the four groups of patients (only NSAIDs, only ASA,
NSAIDs in combination with ASA, and no known use of
NSAID/ASA). Neither the endoscopic nor the histological
findings differed among these four groups; this might indicate
either that the patients in the no NSAID/ASA group often
simply denied using such medication, or that the physicians
had not questioned the patients specifically about over-the-
counter painkillers.

Our retrospective study should prompt a prospective
study. Ideal would be a prospective colonoscopic investigation
of patients taking NSAIDs, with consideration being given
to the nature and duration as also of the galenic formulation
of the preparations employed. Of particular interest would
be an investigation of the side effects of COX-1 inhibitors
in comparison with COX-2 inhibitors, which also can cause
lesions in the lower GIT[51,53]. Only in this way could we
obtain data on the incidence, localization and type of lesions
as a function of the medication. Such a study in patients
with no colon-specific symptoms would, however, hardly
be ethically justifiable. Worthy of discussion, however, is
the question whether, in patients on NSAIDs, a hemocult
test could be performed and, in the event of positive results,
an indication for colonoscopy established. Also, an investigation
of the incidence of NSAID-induced lesions in the small
intestine employing capsule endoscopy should receive
consideration.

What the results of our retrospective study definitely
show, however, is that the pathologist who finds focal
erosions, ulcers and strictures, together with necroses of
the ischemic type in biopsies from the (mainly right) colon,
should, more than previously, suggest in his report the
possibility of an NSAID-induced mucosal injury. This would
then prompt the care-providing physician to look into the
patient's use of NSAIDs, the type of preparation employed,
its dosage and galenic formulation, and then possibly replace
or discontinue the medication with the aim of clarifying the
etiopathogenesis of the lesion and preventing such serious
complications such as perforation, chronic bleeding, and
strictures. In principle, however, the NSAID/ASA-induced
lesions cannot be differentiated histologically from ischemic
lesions. This, too, should be emphasized in the histological
report. Although arteriosclerosis-induced ischemic colitis is
usually located in the left colon, and often manifests as
multiple lesions distributed over a large area, other rare
causes of ischemic colitis (e.g., vasculitis, distension colitis,
embolii) may also give rise to irregularly distributed focal
lesions at atypical locations. In our experience as consultant
pathologists investigating biopsy and surgical material, the
most common endoscopic and histological wrong diagnosis
in NSAID-induced colonopathy is Crohn's disease established
on the basis of the discontinuous changes due to NSAID
colonopathy. This diagnostic error can, however, be avoided
by giving consideration to the age of the patient, since
NSAID-induced colonopathy is seen mainly in the elderly
people. However, also in the case of young patients with

| NSAID (%) | n = 22 | n = 17 | n = 101 | n = 30 | n = 17 |
| NSAID+ASA (%) | n = 16 | n = 9 | n = 16 | n = 6 | n = 8 |
| ASA (%) | n = 16 | n = 34 | n = 34 | n = 32 | n = 6 |
| No NSAID/ASA (%) | n = 4 | n = 10 | n = 7 | n = 19 | n = 5 |

Table 10 Frequency of histological findings in the four groups of patient
no other clinical and laboratory findings suggestive of Crohn’s disease, the physician should be prompted to enquire about the use of NSAIDs, and if such use is denied, to apply ASA serology to test for possible misuse of painkillers[54].

In conclusion, the present study shows that our retrospective suspected diagnosis of NSAID/ASA-induced enterocolitis, the physician should be prompted to enquire about the use of NSAIDs, and if such use is denied, to apply ASA serology to test for possible misuse of painkillers[54].

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