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## SIGNIFICANCE OF SALICYLATE INTOLERANCE IN DISEASES OF THE LOWER GASTROINTESTINAL TRACT

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Salicylate intolerance is defined as a nonspecific antigen-induced pseudo-allergic hypersensitivity reaction which can occur upon contact of an organism with salicylic acid, its derivatives or other related organic or inorganic acids of similar chemical structure. Since the effects of nonsteroidal anti-inflammatory drugs (NSAID) intolerance are by no means always severe or life-endangering but may just as well present as oligosymptomatic or local disorders (e.g. abdominal pain, diarrhea, we decided to evaluate the characteristics of patients with salicylate intolerance on the basis of gastroenterological case material of Medical Department I of Erlangen University. On the basis of the findings from the Erlangen interdisciplinary data register of chronic inflammatory gastrointestinal disease, the signs and symptoms of NSAID intolerance were found to constitute a diagnosis of great practical import to clinical medicine (allergology, dermatology, immunology, other disorders etc.) including gastroenterology. For approx. 2-7% of all patients with inflammatory bowel syndrome and food allergies this poses a new diagnostic and therapeutic challenge which may concern physicians from any of the disciplines involved. When presented with patients with chronic active disease who are suffering from these symptoms one should, therefore, in future give greater thought to the possibility of salicylate intolerance, all the more as there are meaningful dietetic, diagnostic and therapeutic options available for these persons.

Key words: *salicylate intolerance, lower gastrointestinal tract*

## INTRODUCTION

Salicylate intolerance is defined as a nonspecific antigen-induced pseudo-allergic hypersensitivity reaction which can occur upon contact of an organism with salicylic acid, its derivatives or other related organic or inorganic acids of similar chemical structure (1, 2) . The spectrum of salicylate intolerance (NSAID intolerance) triggers comprises not only aspirin, nonsteroidal antiphlogistics and other salicylate-containing drugs but also certain foods containing salicylic acid in various concentrations, preservatives and colorants. Since this type of pseudo-allergic hypersensitivity reaction is not limited to one specific substance (such as aspirin) but can be triggered by any of a whole group of substances it is preferable to speak of NSAID intolerance rather than salicylate intolerance (1).

Although many people come in contact with the above-named groups of substances, the exact frequency of salicylate intolerance in the population is still not known to date. NSAID intolerance is observed more frequently in adults than it is in children, and this is taken as an indication of its being an acquired disorder (pseudo-allergy) (1). First reports of frequency data have now become available for certain patient groups. For example, 2 to 4 per cent of patients being treated at allergology outpatient clinics are found to be NSAID intolerant (1). Among the patients of otorhinolaryngology clinics 15 to 20 per cent of those with chronic rhinitis, nasal polyps, sinusitis and nonallergic asthma are also found to be intolerant to salicylate. In the area of gastroenterology, reliable systematic data on the incidence of salicylate intolerance have not been reported to date. In view of the fact that certain groups of gastroenterological disease (e.g. IBD = Inflammatory Bowel Disease) are treated with salicylate containing drugs, the issue of NSAID intolerance in these patients is of great clinic significance, especially as regards differential diagnostics (3-7).

The clinical picture of salicylate intolerance (NSAID intolerance) is characterized by systemic as well as local (oligosymptomatic) manifestations. The classical triad of intolerance to acetylsalicylic acid (ASA triad) comprises the occurrence of polyposis nasi, nonallergic asthma and angioedema as well as laryngeal edema following contact with substances containing acetylsalicylic acid (1,2). Angioedema, laryngeal edema and asthma attacks are often manifestations of an acute pseudo-allergic episode, whereas polyposis nasi and chronic sinusitis can be a chronic sequel of an unrecognized salicylate intolerance. *Table 1* shows further systemic (typical), local or oligosymptomatic (atypical) symptoms of salicylate intolerance, all of which may be of an acute or chronic nature (2-7).

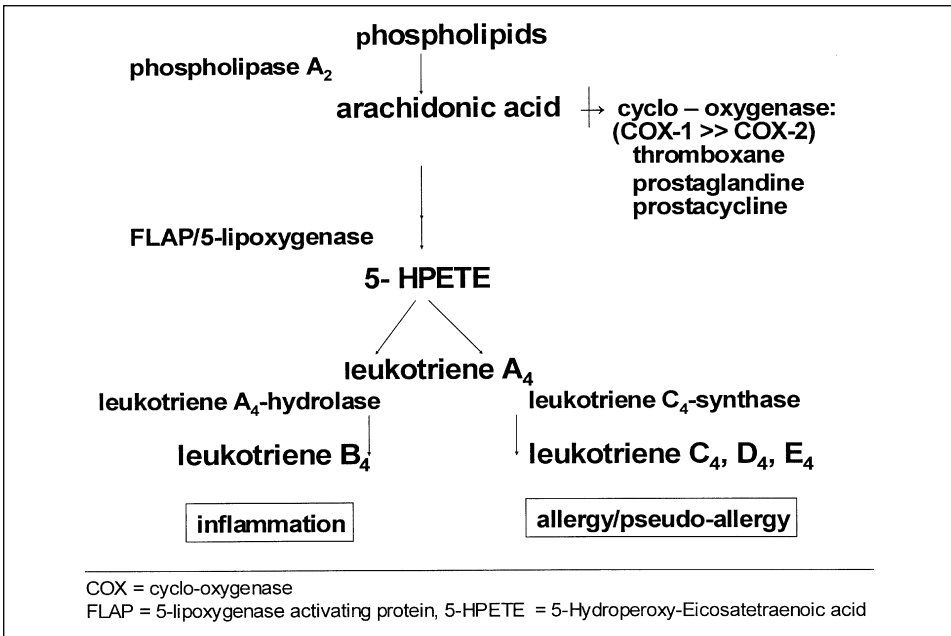
In distinction from systemic symptoms, which constitute a general immune response of the entire organism, there may also be local symptoms in the gastrointestinal tract. To date there has been no specific research on the question why in some persons NSAID intolerance manifests itself in a general systemic

Table 1. Acute und chronic pseudoallergic disease manifestations resulting from salicylate intolerance (NSAID-intolerance)

<p><b>I Systemic manifestations, acute or chronic</b></p> <p>angioedema*, larynx edema            asthma bronchiale*            chronic urticaria            fever, generalised pruritus            recurrent nose swelling, secretion, rhinorrhea            sinusitis &amp; polyposis nasi*                rare manifestations            shock, death            myocarditis, pericarditis, interstitial nephritis, pulmonal infiltrates etc.</p> <p>* ASA - Triad: Mygind N. Allergology: Textbook &amp; Atlas, Blackwell Verlag 1998; pp.64- 66</p>											
<p><b>II Gastrointestinal manifestations, acute or chronic</b></p> <table border="0"> <tr> <td>acute phase</td> <td>late or chronic phase</td> </tr> <tr> <td>erosion, meteorism</td> <td>fibrosis, strictures, (fistula ?<sup>4</sup>)</td> </tr> <tr> <td>pain<sup>2</sup>, edema, swelling<sup>4</sup></td> <td></td> </tr> <tr> <td>ulcera<sup>1-3</sup></td> <td></td> </tr> <tr> <td>diarrhea<sup>2</sup>, colitis<sup>1-3</sup></td> <td></td> </tr> </table> <p><sup>1</sup>Werlin SL. J Paediatr 1978; 92: 450-451, <sup>2</sup>Pearson DJ. Br Med J 1983; 287: 1675,  <sup>3</sup>Chakraborty TK. Gut 1987; 28: 613-615, <sup>4</sup>Pearson M. Gut 1993; 34: 783-787</p>		acute phase	late or chronic phase	erosion, meteorism	fibrosis, strictures, (fistula ? <sup>4</sup> )	pain <sup>2</sup> , edema, swelling <sup>4</sup>		ulcera <sup>1-3</sup>		diarrhea <sup>2</sup> , colitis <sup>1-3</sup>	
acute phase	late or chronic phase										
erosion, meteorism	fibrosis, strictures, (fistula ? <sup>4</sup> )										
pain <sup>2</sup> , edema, swelling <sup>4</sup>											
ulcera <sup>1-3</sup>											
diarrhea <sup>2</sup> , colitis <sup>1-3</sup>											
<p><b>III Oligosymptomatic manifestations, Cave: atypical, isolated symptoms</b>            from I and/or II</p>											

hypersensitivity while in others it produces symptoms that are more or less local and organ-specific. However, the presentation of such gastrointestinal symptoms, whether or not accompanied by systemic manifestations, can pose considerable difficulties of differential diagnosis, and the possibility of NSAID intolerance should therefore always be drawn into consideration in patients not responding to therapy.

Pathophysiologically speaking, symptoms of salicylate intolerance can be explained by an overproduction of leukotriene metabolites, since salicylate intolerant patients who have come in contact with salicylate containing substances show a marked inhibition of cyclooxygenase (COX-1), which is continuously expressed in the body (*Fig. 1*) (2, 8). On one side this leads to a diminished production of typical cyclooxygenase products (e.g. tissue-protective prostaglandin derivatives, prostacyclin, thromboxan), while on the other it accelerates the metabolization of arachidonic acid towards leukotriene A<sub>4</sub> (9). Leukotriene A<sub>4</sub> undergoes rapid enzymatic conversion, either to leukotriene B<sub>4</sub>, a strong chemotactic agent, or *via* leukotriene C<sub>4</sub> synthase to leukotriene C<sub>4</sub>. This product can then be decomposed to leukotrienes D<sub>4</sub> and E<sub>4</sub>. Leukotrienes C<sub>4</sub> through E<sub>4</sub> are collectively referred to as SRS (slow reacting substances of



*Fig. 1* Eicosanoid metabolism and the mechanism of NSAID-intolerance

anaphylaxis) (8,9). The variety of symptoms of salicylate intolerance in a tissue or person may be explainable by different expression rates or differences in the control and/or activation of leukotriene A<sub>4</sub> hydrolase or leukotriene C<sub>4</sub> synthase. The leukotriene B<sub>4</sub> path is primarily involved in maintaining inflammatory processes (e.g. chronic colitis), whereas the leukotriene C<sub>4</sub> path is more involved in triggering typical pseudo allergic mechanisms (e.g. angioedema, asthma, urticaria) (1,8,9). This differentiation into a largely proinflammatory leukotriene B<sub>4</sub> path and a largely pseudo-allergic leukotriene C<sub>4</sub> through E<sub>4</sub> path finds its continuation in a differentiation of receptors by which these effects are mediated. (cys-L T - B<sub>4</sub>R and cys- L T - D<sub>4</sub>R, (9)). Both these leukotriene receptors are G protein coupled membrane proteins, yet they are responsible for different manifestations of salicylate intolerance. Leukotriene B<sub>4</sub> is considered to act as a strong chemotactic signal ( of similar strength as complement factors). It activates T8 suppressor cells, inhibits T<sub>4</sub> helper cells and is supposed to stimulate IgE synthesis. The main leukotriene receptor mediated effects of leukotrienes C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub> are bronchoconstriction, bronchial hyperreactivity, mucus production and vasodilatation (1). Furthermore, both leukotriene groups are thought to act as powerful contractors of nonvascular smooth musculature (1, 8, 9).

Since the effects of NSAID intolerance are by no means always severe or life-endangering but may just as well present as oligosymptomatic or local disorders

( e.g. abdominal pain, diarrhea (2,5), (Table 1), it was decided to evaluate the characteristics of patients with salicylate intolerance on the basis of gastroenterological case material of Medical Department I of Erlangen University (MS - Access database, interdisciplinary data register of chronic inflammatory and allergic bowel diseases).

## MATERIALS AND METHODS

### *Patients*

From a source population of 1097 fully documented cases entered into the interdisciplinary data register of chronic inflammatory and allergic gastrointestinal diseases over the past 8 years an extract was made of those containing any of the terms “aspirin intolerance”, “salicylate intolerance” and “NSAID intolerance”. The subset thus obtained was classified into the disease groups ulcerative colitis, gastrointestinally mediated allergy (GMA), Crohn's disease and a control group consisting of patients with carbohydrate malabsorption or irritable bowel syndrome. Intolerance diagnoses of any of the three types named above were only accepted if there were records prepared by a physician documenting the occurrence of clinically manifest symptoms following the intake of aspirin, salicylates (e.g. mesalazine) and/or other nonsteroidal antiphlogistics and this was additionally confirmed by a physician's original findings. Persons suspected of having NSAID intolerance were tested either by oral single-blind placebo-controlled aspirin provocation or by mesalazine provocation. In many cases this was supplemented by a blood test for leukocyte eicosanoid production (10). The demographic, clinical and laboratory chemical characteristics of these patients were systematically evaluated on the basis of the patient records present.

Diagnoses of grade I to IV gastrointestinally mediated allergies (GMA) were considered valid if confirmed by oral double-blind placebo-controlled provocation tests (11,12), while diagnoses of IBD were verified on the basis of established clinical, endoscopic, histological, radiological and laboratory chemical characteristics ( 13,14).

Five persons (4 cases of ulcerative colitis, 1 case of Crohn' s disease) undergoing single-blind provocation with mesalazine (500 mg Pentasa capsules) were additionally monitored for urinary methylhistamine over the entire test duration (5 - 7 days).

The protocol and informed consents were reviewed and approved by Institutional Ethical Committee at Erlangen-Nuremberg, Germany and informed consent was obtained from each patients.

### *Immunological mediator diagnostics*

Urinary methylhistamine excretion was determined by patients collecting 12-hour night urine (18:00- 06:00 hrs) while on a normal balanced or mixed diet that was known to cause the relevant complaints followed by a low-allergen elimination diet (e.g. potato and rice diet, tea and mineral water, later a rice-only or potato-only diet) (15-17). Balanced diet (day 1-2) and low-allergen meals (day 3-4) as well as rice-only and potato-only meals were only allowed to be taken until 2 p.m. (15,17). After that the patient ate no more until the next morning (tea and mineral water permitted). The urine monitoring was accompanied by a documentation of clinical symptom scores in the course of the collection days. Urine was treated with 10% acetic acid and submitted to the Buchwald-Schultis laboratory for methylhistamine measurement by tandem mass spectroscopy (Weiden/Bavarian, Germany) (sensitivity 2.6 ng/ml, intraassay and interassay variation 3.2 and 4.1%). In view of the fact that mediator values vary considerably between individuals, methylhistamine excretion values were

standardized by setting them in relation to creatinine excretion and body surface area (15-17). Furthermore, mediator values were determined as average values for each 2-day diet phase (15).

The clinical and laboratory chemical parameters under study were evaluated statistically by descriptive methods (frequencies) and by calculating means and standard deviations. Significance calculations were based on the Mann - Whitney test, and outcomes with  $p < 0.05$  were declared significant.

## RESULTS

### *Frequencies of NSAID intolerance in major gastroenterological diseases*

As *Table 2* shows, a small percentage of those patients with a major gastroenterological disease showed a NSAID intolerance that was either clinically well-documented or confirmable by provocation. According to the present literature, NSAID intolerance is most frequently associated with ulcerative colitis and GMA, whereas only 2.1% of patients with Crohn's disease are intolerant to salicylate.

### *Major laboratory chemical and clinical parameters in the NSAID intolerant patient groups*

In terms of the basic laboratory chemical parameters such as erythrocyte sedimentation rate, eosinophils and serum IgE, NSAID intolerant patients showed no clear trend towards pathologically altered laboratory values (*Table 3*). An interesting finding in the clinical parameters is that mesalazine medication was ineffective in more than half of ulcerative colitis patients with salicylate intolerance. Further possible indicators of salicylate intolerance include patient reports of intolerance to (developing complaints from) aspirin, mesalazine or potatoes, since in the disease groups under study 14- 40% of NSAID intolerant patients reported complaints of this type.

*Table 2* Frequency of NSAID - intolerance from the Erlangen interdisciplinary data register of chronic inflammatory and allergic bowel diseases

disease group	total number (n = patients)	clinically documented NSAID-intolerance (n = patients or %, respectively)	confirmed by challenge NSAID-intolerance (n = patients or %, respectively)	total sum NSAID-intolerance (%)
Crohn's disease	332	6/332 (1.8%)	1/332 (0.3%)	7 (2.1%)
ulcerative colitis	215	9/215 (4.2%)	7/215 (3.2%)	16 (7.4%)
GMA	374	12/374 (3.2%)	10/374 (2.7%)	22 (5.9%)
carbohydrate malabsorption, colon irritabile etc.	176	1/176 (0.6%)	-	1 (0.6%)

Table 3 Clinical and laboratory characteristics of NSAID - intolerant patients

	Crohn's disease 7/332	ulcerative colitis 16/225(5.9%) (5.9%)	GMA 22/374 (5.9%)	carbohydrate malabsorption, colon irritable etc. 1/176 (0.6%)
<b>history and clinical data</b>				
atopy	3/7 (42.8%)	8/16 (50.0%)	10/22 (45.4%)	0/1 (0.0%)
abdominal pain, diarrhoe from 5-ASA/aspirin	1/7 (14.2%)	6/16 (37.5%)	7/22 (31.8%)	1/1 (100.0%)
5-ASA ineffective	2/7 (28.6%)	10/16 (62.5%)	-	-
adverse reaction to potato	2/7 (28.6%)	4/16 (25.0%)	9/22 (40.9%)	0/1 (0.0%)
<b>important laboratory and immunological parameters</b>				
erythrocyte sedimentation rate (mm 1 hour) N: < 10	14 ± 18	12 ± 11	5±3	2
eosinophils (n/μl) N: < 400	420 ± 210	510 ± 86	440 ± 204	384
serum - IgE (KU/L) N: < 100	66.7 ± 113	108 ± 225	76 ± 94	32

*Mediator diagnostics based on methylhistamine excretion in NSAID intolerant patients with gastrointestinal allergy under different diets*

In 9 of 22 (40.9%) patients with confirmed gastrointestinal allergy and salicylate intolerance it was possible to measure urinary methylhistamine excretion during the diet phases of unrestricted diet, potato and rice diet and potato-only or rice-only diet. MA patients showed clearly elevated urinary methylhistamine levels while on a unrestricted diet, regardless of whether they were salicylate tolerant or intolerant. One remarkable finding is that salicylate tolerant allergy patients (disregarding cases of potato or rice allergy, which are rare) show a rapid decrease in methylhistamine production after changing to a hypoallergenic potato and rice diet ( $p = 0.005$  versus unrestricted diet), potato-only diet ( $p < 0.005$ ) or rice-only diet ( $p < 0.006$ ) and eventually reach normal methylhistamine elimination values (Fig. 2), (15), whereas salicylate intolerant patients continue having greatly elevated urinary methylhistamine values after changing to the potato and rice diet ( $p = 0.08$  versus unrestricted diet) or to the potato-only diet ( $p = 0.06$ ). Salicylate intolerant patients only return to normal methylhistamine elimination values after changing to a rice-only diet ( $p = 0.008$ ). The complaints reported by the 9 salicylate intolerant allergy patients (40.9%) when on a potato and rice or potato-only diet are therefore partly

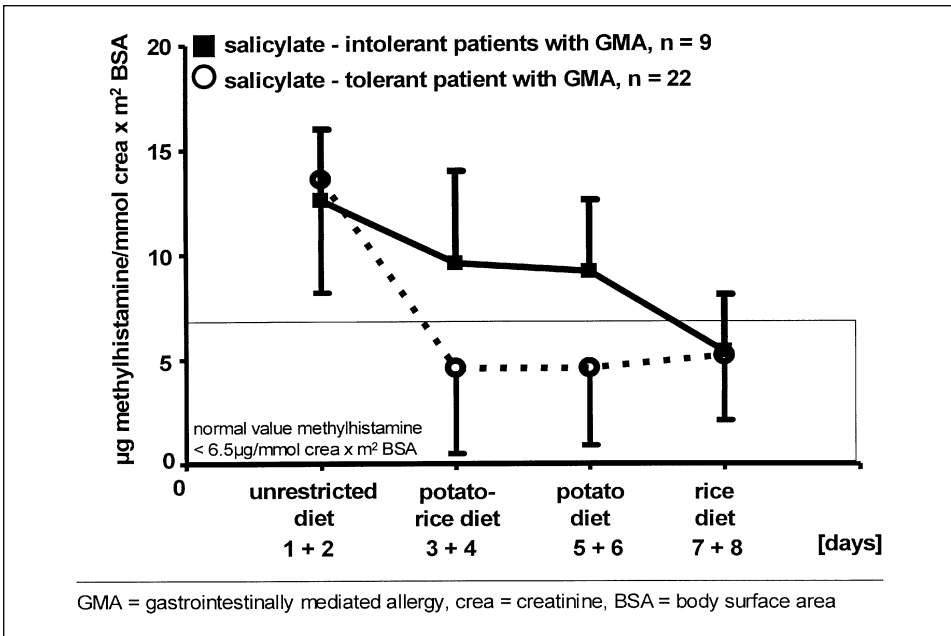


Fig. 2 Methylhistamine production in patients with gastrointestinally mediated allergy (GMA) with and without salicylate intolerance (NSAID-intolerance)

attributable to the effects of the elevated methylhistamine production which results from the salicylate content of potatoes.

*Mediator diagnostics based on methylhistamine excretion in NSAID intolerant patients with chronic IBD following single-blind oral provocation with mesalazine*

Five persons with chronic IBD and associated salicylate intolerance gradually developed clinical complaints starting on the second day of oral application of 3 x 500 mg mesalazine daily. 2 of 5 patients (40%) developed abdominal pain from test day 2 onward. From test day 3 on this was compounded by an increase in stool frequency (3 of 5 persons; 60%), flatulence (2 of 5 persons; 40%) and pruritus (1 of 5 patients; 20%). From test day 4 on stools not only became more frequent but also more liquid/diarrhetic (4 of 5 patients; 80%).

The observed kinetics of urinary methylhistamine elimination yielded further evidence of an involvement of methylhistamine in the pathology of salicylate intolerance, since provocation with mesalazine resulted in an increase in methylhistamine elimination around significance threshold through to test day 5 (Fig. 3). Starting from an elevated baseline average, expressed in terms of µg/mmol creatinine x m² body surface area, methylhistamine production rose from  $8.7 \pm 5.2$  to peak values of  $12.8 \pm 8.5$  ( $p = 0.07$ ).



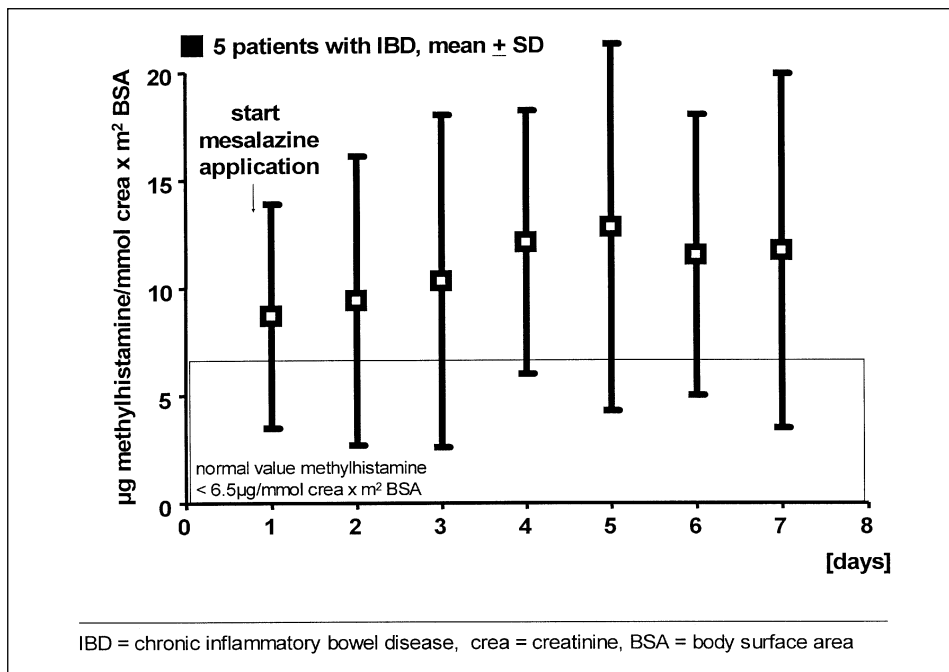


Fig. 3 Methylhistamine production in chronic Inflammatory Bowel Disease and NSAID intolerance during oral mesalazine challenge

## DISCUSSION

Although reports and case collections on salicylate intolerance in patients with gastroenterological diseases have been available since the early 1970s (3-5, 18), there have to date been no systematic studies on the frequency of NSAID intolerance in the field of gastroenterology. In a control group with carbohydrate malabsorption or irritable bowel syndrome which had been extracted from the Erlangen interdisciplinary data register of chronic inflammatory gastrointestinal disease on the basis of the three criteria clinically well documented intolerance reaction to NSAID, aspirin and/or mesalazine, proof of a clearly pathologically elevated leukotriene production in peripheral blood cells (10) and proof of intolerance by single-blind mesalazine provocation, the frequency of NSAID intolerance was found to be 0.6%.

The rate of NSAID intolerance in cases of Crohn's disease was found to be 2.1 %, whereas in persons with gastrointestinal allergy or ulcerative colitis this condition was found far more frequently, at rates of 5.9% and 7.4%, respectively. On systematic evaluation these data thus show that the wide spectrum of NSAID intolerance is also of significance to gastroenterology and should be more carefully taken into account (3, 7, 8, 18, 19). This applies not only to IBD, which

is often treated with 5-aminosalicylic acid preparations, but probably also to microscopic colitides as well as to certain reported cutaneous, pulmonic and gastroenterological intolerance reactions (17-19). For NSAID intolerance is not only associated with the known intolerance reactions following the ingestion of aspirin, NSAID or mesalazine; it can also lead to symptoms from salicylates that are naturally contained in foods (pineapple, berries, curry, spices, potatoes, citrus fruits etc.), from food additives, preservatives and colorants with a chemical structure similar to that of salicylic acid (e.g. benzoic acid, tartrazine etc. (1,19)) and even from drugs with similar organic acid structures (e.g. disodium cromoglycic acid). The last named substance can cause considerable confusion in the differential diagnostics and treatment of allergic gastrointestinal diseases. Exacerbation of abdominal pain or diarrhea following the intake of disodium cromoglycate (acid) or mesalazine is therefore seen as a clear indication for a thorough examination for NSAID intolerance.

The standard diagnostic procedure consists in progressive oral provocation with aspirin or mesalazine starting with a dose adjusted to the severity of the reported intolerance symptoms (e.g. 100 - 250 - 500 mg lysine-aspirin or 250 - 500 - 1000 mg mesalazine (1,2)). It is well known that such provocative treatment can cause life-endangering reactions (e.g. acute bronchospasm, generalized flush/urticaria, hypotension etc.), and it should therefore only be performed at inpatient facilities by duly trained and experienced physicians. Whereas acute systemic or nasal, pulmonic or vascular reactions may take only a few hours to develop, chronic, organ-related symptoms such as gastroenterological or other oligosymptomatic manifestations (e.g. abdominal pain, diarrhea, pruritus etc.) may still appear after several test days (1, 2, 4, 8). As an alternative to oral provocation it is also possible to use a blood test for eicosanoid production in peripheral blood cells to identify persons with NSAID intolerance (10). If the observed clinical reactions and symptoms are in agreement with the anamnestic findings and the blood test shows a significant increase in leukotriene production in peripheral blood cells after adding of 5-aminosalicylic acid or lysine-aspirin to the leukocyte preparation, then *in vivo* oral provocation testing with all its complex monitoring procedures attains no more than a confirmatory role. Oral provocation testing should therefore only be used in cases where a discrepancy is found between the anamnestic findings, clinical symptoms and/or the peripheral blood cell test.

When patients show clinical signs of NSAID intolerance such as intolerance to aspirin, ineffectiveness or aggravation of symptoms after administration of mesalazine or complaints after ingestion of salicylate-containing foods (e.g. potatoes) and their complaints manifest themselves as symptoms of the ASA triad (angioedema, nonallergic bronchial asthma polyposis nasi), this should prompt an examination for salicylate intolerance (1-3, 8). Many routine laboratory parameters such as blood picture, eosinophils, erythrocyte sedimentation rate or serum IgE levels are not helpful in identifying NSAID intolerance as a functional disorder of the eicosanoid metabolism. The only indication that a IBD patient's

recumng complaints may not attributable to the underlying inflammatory disease but to other causes (e.g. postinflammatory stricture, small bowel intestinal bacterial overgrowth) and/or the manifestation of an oligosymptomatic salicylate intolerance may be the absence of an elevated erythrocyte sedimentation rate - a frequent phenomenon - or of inflammatory processes (e.g. C reactive protein, protein electrophoresis). In cases where IBD complaints persist in absence of any observable inflammatory process it may take a specific anamnesis for tolerance of aspirin and/or any of the above-named foods, temporary interruption of 5-amino salicylate medication or peripheral blood tests for leukotriene production to obtain the first substantial indication of NSAID intolerance. Far from being only of academic interest to IBD patients, the discovery that they are NSAID intolerant can be very significant for their long-term prospects. Today there are effective desensitization methods available, which are used successfully in interdisciplinary therapies performed in cooperation with allergologists or immunologists (1, 20-25). One implication of this, for example, is that patients with ulcerative colitis need no longer be deprived of effective anti-inflammatory treatments, which also reduce their risk for dysplasia. Furthermore, by making a targeted search for NSAID intolerance one can avoid putting patients with chronic active disease caused by salicylate intolerance (absence of inflammation) on immune suppressive medication (e.g. azathioprine, cyclosporine) without a justifiable indication for this. IBD patients with NSAID intolerance who do not wish to be desensitized to aspirin (e.g. patients with stomach disorders) or mesazaline still have therapeutic alternatives at their disposal such as leukotriene receptor blocker medication for conservative treatment or E. coli preparations in ulcerative colitis.

Another indirect yet objective parameter for recognizing NSAID intolerance is, perhaps surprisingly, the level of urinary methylhistamine. For although methylhistamine excretion is an unspecific parameter, all persons with IBD and salicylate intolerance showed a moderate increase in methylhistamine and a gradual progression of symptoms upon mesazaline provocation. Since NSAID intolerance is known to be associated with a disturbance of the eicosanoid metabolism with inhibition of cyclooxygenase 1, one would expect the measurement of urinary leukotriene excretion to yield a far more clearly pathological mediator profile than the measurement of methylhistamine, as is the case with salicylate intolerant asthma patients (2, 8, 19). Possibly the increase in urinary methyl histamine in NSAID intolerance can be explained as an accompanying phenomenon of the elevated production of leukotriene B<sub>4</sub> and/or leukotrienes C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>, since the strong inflammatory and chemotactic effects of leukotriene B<sub>4</sub> and the permeability increasing effects as well as allergic, inflammatory effects of leukotrienes C<sub>4</sub> - E<sub>4</sub> can result in an activation of histamine-containing cells (mast cells, eosinophils) as well as of immune cell populations that interact with mast cells (e.g. eosinophils, T cells etc. (9, 10, 26-29). Furthermore, mast cells, basophils and eosinophilic granulocytes, on account of their capacity to produce leukotrienes, are regarded as the chief effector cells

implicated in NSAID intolerance (1, 25, 26), and atopic persons have an especially elevated risk for developing NSAID intolerance (25).

These facts are also reflected in the persistently high rate of methylhistamine excretion in patients with gastrointestinal allergy and salicylate intolerance who are on a salicylate containing diet. For NSAID-intolerant and allergic patients only show a recovery from pathologically elevated methylhistamine production back to the normal range when they abstain from potatoes and the salicylate they contain. Since person with food allergies have an enlarged pool of mast cells, eosinophils and basophils, this effect is particularly visible in their methylhistamine excretion rates. Persistently high methylhistamine excretion rates in persons on a potato/rice diet or a potato-only diet are therefore considered an important indication today for excluding a rare potato or rice allergy and/or for salicylate testing. Since NSAID intolerance in persons with food allergies poses an additional dietetic challenge, including abstention from salicylate-containing foods (e.g. pineapple, berries, curry, spices, potatoes, citrus fruits etc.) as well as food additives (colorants and preservatives (1, 8, 19), one should always consider the therapeutic option of an interdisciplinary desensitization program for these persons, similarly to cases of IBD. However, continuous administration of salicylates (e.g. long-term aspirin therapy) promotes the resorption of allergens from the gastrointestinal tract, and any salicylate desensitization treatment should therefore be preceded by an accurate diagnosis of the triggering allergens, for example by double-blind oral provocation or ex vivo biopsy testing (12). Salicylate desensitization can only bring about sufficient symptom relief if accompanied by consistent abstention from allergens.

Speaking on the basis of our findings from the Erlangen interdisciplinary data register of chronic inflammatory gastrointestinal disease, the signs and symptoms of NSAID intolerance constitute a diagnosis of great practical import to clinical medicine (allergology, dermatology, immunology, other disorders etc.) including gastroenterology. For approx. 2- 7% of all patients with IBD and food allergies this poses a new diagnostic and therapeutic challenge which may concern physicians from any of the disciplines involved. When presented with patients with chronic active disease who are suffering from these symptoms one should therefore in future give greater thought to the possibility of salicylate intolerance, all the more as there are meaningful dietetic, diagnostic and therapeutic options available for these persons.

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