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# ASA-induced release of histamine from nasal mucous membranes in analgesic intolerance and polyposis nasi

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SUMMARY

*Tissue samples from the polypous mucous membrane and the inferior nasal concha were taken from 13 patients with polyposis nasi and from 12 other patients with an additional intolerance to analgesics. The tissue of the inferior nasal concha from patients without polyposis nasi served as a control. The relative histamine content of the samples (in ng/mg dry weight) and the relative histamine release (in %) after addition of acetylsalicylic acid (ASA) were determined. A significantly higher relative histamine content in the tissue samples of polyp patients without an intolerance to analgesics was seen in comparison to the other two groups. The relative histamine release of both patient groups with nasal polyposis was comparable. The control group exhibited both an increased spontaneous release of histamine as well as a higher relative histamine release from the tissue of the inferior nasal concha.*

In the course of surgical treatment of the diffuse polyposis nasi an existing intolerance of analgetics (Non-steroidal anti-inflammatory drugs = NSAID) represents an important risk factor for therapeutic failure (Loewe et al., 1985; Hosemann et al., 1988). According to anamnesis this subgroup represents 9.5% of the total number of patients with polyposis nasi. Slapke and Hummel (1988) pointed out the difficulty of diagnosing this intolerance based solely on case history details. Rhinitis or polyposis nasi usually occurs before the analgesic intolerance is known (Virchow and Schmitz-Schumann, 1986). If no analgetics are administered, subclinical forms of intolerance or manifest clinical pictures may be overlooked by doctor and patient. Therefore, the special clinical significance of an analgesic intolerance diagnosis is the basis of different test procedures, particularly challenge tests (e.g. Rosenhall, 1982). Challenge tests, however, are complicated and not without risks.

In order to find possibilities of diagnosing in-vitro analgesic intolerance and of examining pathophysiological correlations between intolerance and nasal polyps, a series of experiments with tissue samples was carried out.

## PATIENTS AND METHODOLOGY

Three groups of patients were examined:

1. A group of 12 patients with polyposis nasi (six women, six men, ages 29 to 54), in which the case histories reported a definite respiratory intolerance reaction (dyspnoea, asthmatic attack up to anaphylactic shock) within a few minutes up to a few hours after taking an acetylsalicylic acid (ASA) preparation.
2. A group of 13 patients with polyposis nasi (two women, 11 men, ages 17 to 64), in which a respiratory intolerance reaction to ASA could be excluded from the case history.
3. A group of eight patients without polyposis nasi, however, with a deviation of the external and/or internal nose. Tissue samples were taken, for instance during a rhinoplasty or septal correction. This group consisted of three women and five men, ages 17 to 64. As in group 2, the case histories reported no sign of a respiratory intolerance reaction to ASS.

During the operation on the patients in group 1 and 2, a polyp of the main nasal cavity and a macroscopically normal piece of mucous membrane was taken from the inferior nasal concha and immediately dissected into several pieces equal in size. From the patients in group 3, of course, only an unchanged piece of mucous membrane could be obtained in the same way. The pieces of tissue were immediately incubated in small glass tubes with Hank's solution. These glass tubes were in turn placed in a transportable water bath (37° C) and oxigenated. ASA was then added; the final concentration in one test series was 0.5 x 1/1000, 0.5 x 1/100 000 and 0.5 x 1/10 000 000 mol/l. Before and after adding ASS an excess quantity was taken from every sample at intervals of 1, 3, 5 and 10 minutes, and placed in a water bath at 95° C to deactivate the enzymatic impurities. The remaining volume was deepfrozen at –20° C for a maximum of 10 days to release the rest of the histamine by destruction of cell membrane.

The histamine in the test solutions was then determined by means of a radio-enzymatic assay modified after Subramanian et al. (1978) and Verburg et al. (1984 a, b). By means of an especially created data program both the total histamine content and the relative release of the samples were determined. This was followed by the determination of the relative histamine content after lyophilization of the pieces of tissue.

The total histamine content (in ng) corresponded with the sum of the histamine values of the excess quantities and the content of histamine in the remaining volume with the tissue sample. The relative release of histamine (in %) coincided

with the release of histamine up to 10 minutes after the addition of ASA minus the histamine release before the addition of ASA, in reference to the total content of histamine. The relative content of histamine (in ng/mg dry weight) in a tissue sample was calculated from the total histamine content, in reference to the dry weight of the sample.

RESULTS

*1. Relative histamine content of the tissue samples*

The relative content of histamine in the different tissue samples is shown in Figure 1. The relatively high level in both the polypous and the non-polypous tissue in patients without analgesic intolerance (group 2) was noticeable. By contrast, the histamine level of polypous and non-polypous tissue in patients with an intolerance (group 1) is more similar to the control group (group 3). The difference between groups 1 and 2 is just as significant ($\alpha = 0.0001$ in the Wilcoxon test) as that between groups 1 and 3 ($\alpha = 0.0001$).

*2. Relative in-vitro release of histamine from polypous tissue samples after addition of ASA (Figure 2)*

The polypous tissue of patients with or without analgesic intolerance (groups 1

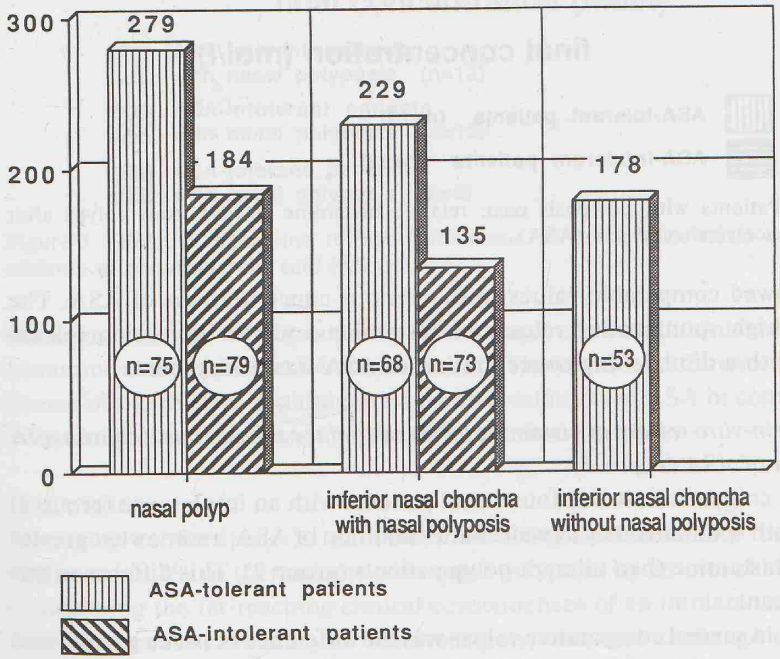


Figure 1. Relative histamine content of various tissue samples (median value in ng histamine/mg dry weight).

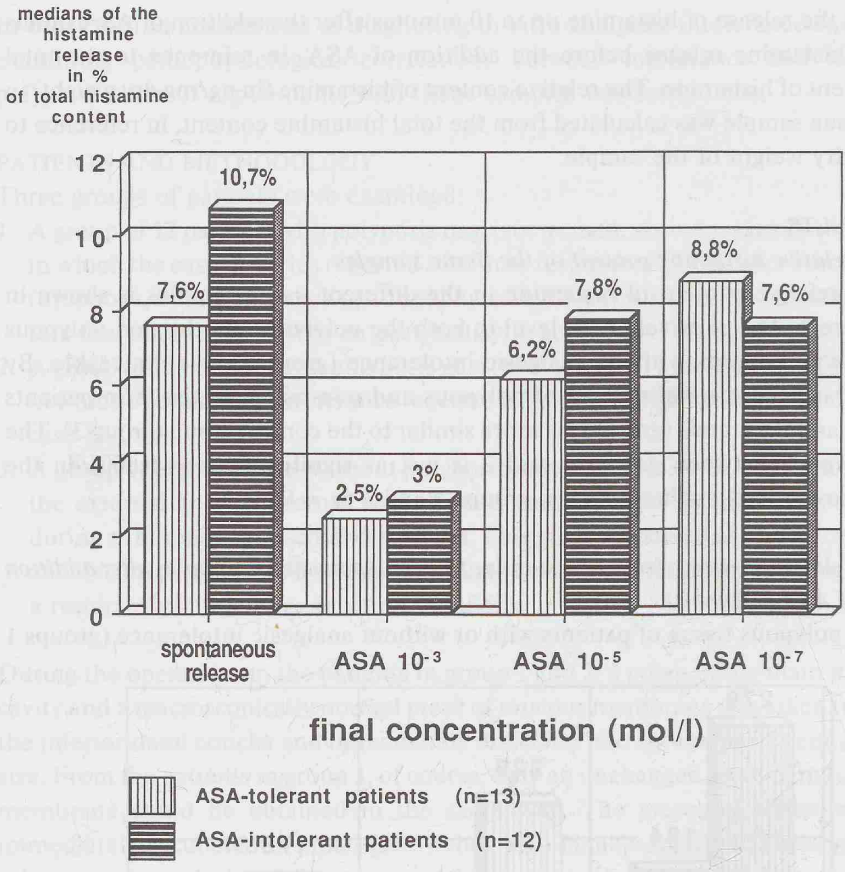


Figure 2. Patients with polyposis nasi: relative histamine release from polyps after addition of acetylsalicylic acid (ASA).

and 2) showed comparable values in the various concentrations of ASA. The relatively high spontaneous release of histamine and the increasing release together with a diminishing concentration of ASA was noticeable.

*3. Relative in-vitro release of histamine from tissue of the inferior nasal concha after addition of ASA (Figure 3)*

By general comparison it was found that patients with an intolerance (group 1) showed, both spontaneously as well as after addition of ASA, a somewhat greater release of histamine than tolerant polyp patients (group 2). This difference was not significant.

Significant in several comparative values was the difference between group 1 and the control group 3 ($\alpha = 0.01$ to 0.005). The latter produced, both spontaneously as well as after the addition of ASA, a relatively high release of histamine.

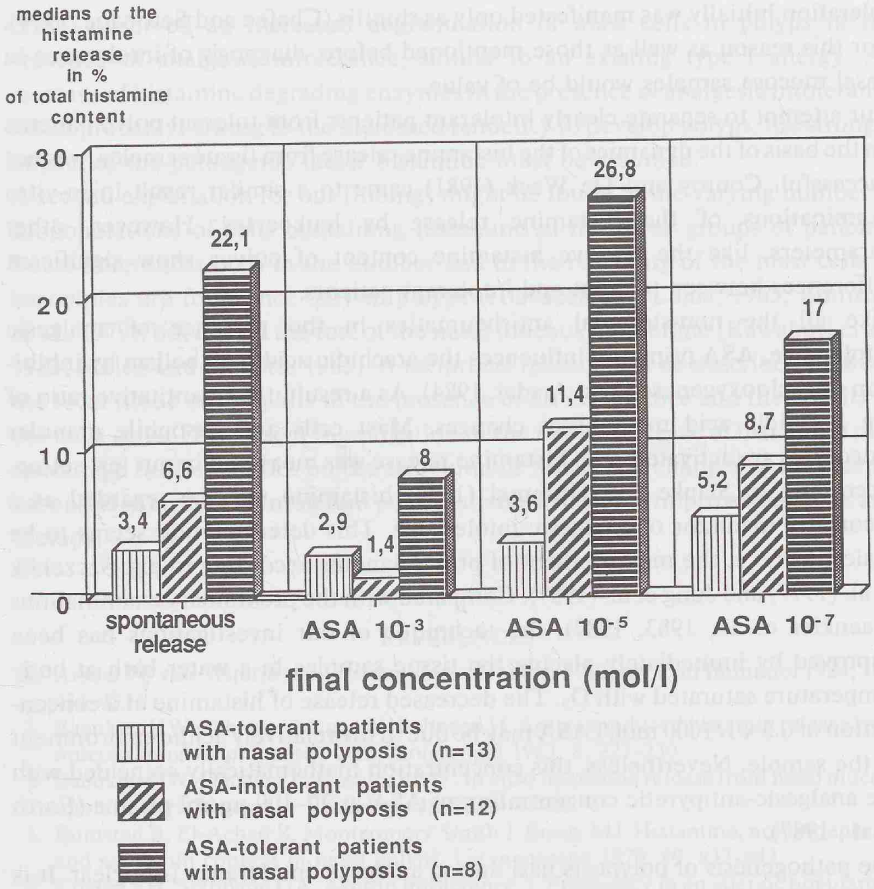


Figure 3. Relative histamine release from tissue of the inferior nasal concha after addition of acetylsalicyclic acid (ASA).

Common to all the three groups of patients was a relatively diminished release of histamine at the highest ASA concentration. There was no difference in the time course of the relative histamine release after addition of ASA in comparison of every subgroup of patients and the different tissue samples.

## DISCUSSION

According to Settipane et al. (1982) an analgesic intolerance can first be diagnosed in 8% of the patients with nasal polyposis by an oral challenge test. Considering the far-reaching clinical consequences of an intolerance diagnosis with its increased tendency to recurrent polyposis, oral challenge tests on all polyp patients would be advisable. These examinations, however, are rather complicated (e.g. Stevenson, 1984). In 10% of the intolerant patients, the lack of

toleration initially was manifested only as rhinitis (Chafee and Settipane, 1974). For this reason as well as those mentioned before, diagnosis of intolerance in nasal mucosa samples would be of value.

Our attempt to separate clearly intolerant patients from tolerant polyp patients on the basis of the dynamics of the histamine release from tissue samples, was not successful. Conroy and De Weck (1981) came to a similar result in in-vitro examinations of the histamine release by leukocytes. However, other parameters, like the relative histamine content of polyps show significant differences between tolerant and intolerant patients.

Like all the non-steroidal antirheumatics in the presence of analgesic intolerance, ASA primarily influences the arachidic acid metabolism by inhibition of cyclooxygenase (Van Arsdel, 1984). As a result, the quantitative ratio of the arachidic acid metabolites changes. Mast cells and basophile granular leucocytes are activated. The histamine release was measured in our test set-up. According to Slapke and Hummel (1988) histamine may be regarded as a secondary mediator of analgesic intolerance. This determination seems to be easier than, i.e. the measurement of prostaglandins according to e.g. Szczeklik et al. (1977) and Jung et al. (1987). Compared with the preliminary examinations (Baenkler et al., 1983, 1987), the technique of our investigations has been improved by immediately placing the tissue samples in a water bath at body temperature saturated with $O_2$. The decreased release of histamine at a concentration of 0.5 x 1/1000 mol/l ASA may be due to the relatively acidic environment of the sample. Nevertheless, this concentration mathematically coincided with the analgesic-antipyretic concentration of ASA at 20–100 µg/ml plasma (Forth et al., 1987).

The pathogenesis of polyposis nasi during analgesic intolerance is unclear. It is not due to an IgE dependent mechanism (Drettner et al., 1985). However, according to Drake-Lee et al. (1982) the increasingly released or less degraded histamine probably plays an essential role. The pathogenic significance of histamine for the proliferation of tissue in the lower respiration tract has also been pointed out (Jordana et al., 1988). Drake-Lee et al. (1984) found no difference in the free histamine content in the extracellular fluid of polyps in patients with or without analgesic intolerance. By contrast our samples showed a significant reduction of the relative histamine content of polyps for an existing intolerance. In agreement with Bumstedt et al. (1979), this may be due to an augmented activity of the mast cells. This condition could be maintained for instance by the daily ingestion of stimulating food additives (Settipane, 1983; Jung et al., 1987). The lower remaining histamine content of the mast cells/basophils could then be the reason for the similar relative histamine release by polyps in patients with or without intolerance. In accordance to this assumption Sasaki (1986) found in polyps, particularly in the polyp stalk, mostly degranulated mast cells. Takasaka et al.

(1986) observed an increased degranulation of mast cells in polyps in the presence of analgesic intolerance, similar to an existing type I allergy. An increase of histamine degrading enzymes in the presence of analgesic intolerance is less probably. Owing to the increased tendency to develop polyps, the stronger impact of the pathogenic factor histamine must be assumed.

A second explanation for our findings might be found in the varying number of subpopulations of cells containing histamine in the three groups of patients. Local differences both in the number and in the reactivity of the mast cells or basophiles are found not only in polyps (Hlavacek and Lojda, 1963; Bumsted et al., 1979), but also in the rest of the nasal mucous membrane (Kawabori et al., 1983; Melen and Pipkorn, 1985). A reciprocal relation can be described between the local tissue eosinophils in the presence of an intolerance and the density of the mast cells. The present investigation of the in-vitro release of histamine may encourage further studies on the structural or functional changes of mast cells/basophils in analgesic-intolerant polyp patients in order to improve diagnosis and therapy.

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