

Potentialiation by Acetylsalicylic Acid of Skin Weal Response to Compound 48/80 in ASA-Sensitive Asthmatics

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The influence of acetylsalicylic acid (ASA) on skin response to intradermal injection of compound 48/80 and histamine was studied in order to determine whether ASA elicits any abnormalities also in the skin of asthmatics reacting with bronchoconstriction to ingestion of this drug.

The applied ASA dose (mean dose 150 mg) elicited bronchoconstriction in all 16 patients with asthma and ASA sensitivity (mean fall of FEV₁ 34%) and increased the weal response to compound 48/80 to about 51% ($P < 0.05$) as compared with the response before the ASA-challenge. In asthmatic persons without ASA sensitivity a 150 mg ASA dose did not influence the skin response to any of the reagents. On the other hand, a 600 mg dose decreased skin response to histamine and compound 48/80 in persons without ASA intolerance, although the decrease was statistically significant only in the flare after compound 48/80 ($P < 0.05$).

The authors believe that additional local defect is needed to reveal sensitivity to ASA in the skin of ASA-sensitive asthmatics, just as bronchial hyperreactivity is indispensable for revealing the action of ASA in the bronchi.

Key words: acetylsalicylic acid; intolerance; mast cells; skin response.

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CLINICAL ASPECTS

During bronchoconstrictor reaction after oral administration of acetylsalicylic acid (ASA) in ASA-sensitive asthmatics a significant increase of weal reaction to intracutaneously given compound 48/80 was observed. It may mean that in ASA-sensitive asthmatics, in whom ASA sensitivity is manifested only as bronchoconstriction, a defect in prostaglandin metabolism concerns also the skin, and is manifested if some additional local damage exists, just as bronchial hyperreactivity related to asthma is needed to reveal ASA sensitivity in the bronchi.

Bronchial obstruction following ingestion of acetylsalicylic acid (ASA) or other nonsteroidal anti-inflammatory drugs (NSAID) is a leading symptom of ASA intolerance in sensitive asthmatics (7, 8). There is convincing evidence that aspirin intolerance in asthmatics is non-immunologic in origin, but depends on the fact that aspirin inhibits cyclooxygenase (10). Prostaglandins seem to modulate bronchomotor tone in asthmatics and also exert a feed-

back controlling effect which inhibits histamine release from mast cells (5, 6). Stevenson et al. (8) reported histamine release into plasma during ASA-induced bronchoconstriction, and in our previous study (11) we also demonstrated mast cell involvement in idiosyncratic reaction to ASA. It is suggested that asthmatic patients with ASA sensitivity may differ from non-sensitive asthmatics by having cyclooxygenase more susceptible to inhibition by NSAID, which may

lead to mediator release from mast cells (9). The postulated abnormality in prostaglandin metabolism in ASA-sensitive asthmatics seems to be a generalized phenomenon found also in organs other than the lungs (1). As we have suggested, the preexistence of bronchial hyper-reactivity is necessary, besides the above-mentioned abnormality, to elicit bronchoconstriction after ASA (12). Similarly, some additional defect in the given organ must exist to evoke extra-bronchial manifestation of ASA-intolerance (3). We decided to simulate in the skin a process typical for asthma, i.e. mast cell degranulation (in our model induced by intradermal (i.d.) injection of compound 48/80) during aspirin challenge in ASA-sensitive asthmatics.

MATERIAL AND METHODS

Subjects

Twenty-three ASA-sensitive asthmatics and 33 asthmatics without ASA sensitivity were studied. ASA intolerance was established from history and confirmed by positive bronchoconstrictor reactions to oral challenge with the drug, performed according to the method reported previously (2). The challenge was performed at least 2 weeks before the beginning of the study.

Skin tests

A tuberculin syringe with a No. 25 gauge needle was used to inject i.d. 0.1 ml of the following reagents: 1) histamine phosphate (0.1 mg histamine base per ml) Sigma Co., 2) compound 48/80 (1 mg/ml) Sigma Co., 3) control solution (0.9% NaCl).

The reagents were injected into the flexor aspect of the forearm at sites at least 5 cm apart. Weal diameters were measured after 15 min in the longitudinal axis of the forearm (a) and at right angles to this (b) and the areas (S) were calculated according to the formula –

$$S = \pi \times \frac{a}{2} \times \frac{b}{2}$$

Flare reactions were measured after 15 min only at right angles to the longitudinal axis of the forearm.

Design to assess effect of ASA on weal and flare response

The patients were tested in the morning after a light breakfast. Bronchodilators had been discontinued for 8 h, steroids and antihistaminics for 72 h and DSCG for at least 3 weeks. Initial skin tests with histamine and compound 48/80 were performed in all patients and only 16 ASA-sensitive and 26 non-sensitive asthmatics were investigated in further experiments with ASA.

ASA-sensitive asthmatics

Initial skin tests with histamine and compound 48/80 were performed in all 23 ASA-sensitive asthmatics. In 16 patients, formerly established provocative doses of ASA were given orally immediately after reading of the 15-min weal and flare reaction on the left forearm. Pulmonary function was measured at 30 min intervals after administration of ASA. When at least a 20% fall in FEV₁ was found the patient was skin tested on the other forearm in an identical manner. No drugs to relieve symptoms of the intolerance were given before the 15-min weal and flare response had been read.

Non-adverse response group (asthmatics without ASA-sensitivity)

After the 15-min weal and flare responses to i.d. histamine and compound 48/80 had been read, 11 patients were given 150 mg and 15 patients 600 mg ASA. 100 min after taking the drug the patients were skin tested on the other forearm (time corresponding with onset of symptoms and skin retesting in ASA-sensitive asthmatics). Spirograms were made before and at 90 and 180 min after the ingestion of ASA.

ASA effect on skin tests

Mean skin weal (areas) and flare (diameters) responses after ASA were compared with the

mean prechallenge (predrug) values. Student's *t* test analysis was employed to determine *P* values for each reagent in each group.

RESULTS

Before administration of ASA the mean areas of weals and mean diameters of flares after i.d. histamine and compound 48/80 did not differ significantly in ASA-sensitive and non-sensitive asthmatics (Table 1).

Oral ASA in ASA-sensitive asthmatics

All patients from this group reacted with bronchoconstriction to formerly established thresh-

old doses of ASA (mean = 154.2 mg, range 20-600 mg) with mean FEV₁ fall of 34% (Table 2). Bronchoconstriction was accompanied by extrabronchial symptoms: rhinorrhea in 11 patients, facial flushing in six and urticaria in one.

Mean time of skin retesting (on the other forearm) corresponding to the onset of bronchoconstriction (at least 20% fall in FEV₁) in a group was 100 min (range 50-180 min).

Oral ASA in ASA-non-sensitive asthmatics

No adverse reactions to ASA (no change in FEV₁) were seen in the group tested with 150 mg ASA or in the group tested with 600 mg ASA.

Table 1

Comparison of the mean weal and flare response after intradermal injection of histamine and compound 48/80 in ASA-sensitive and ASA-non-sensitive asthmatics

Group tested	Patients <i>n</i>	Age in years (mean)	Area of weal in mm ² (mean)		Diameter of flare in mm (mean)	
			After histamine	After compound 48/80	After histamine	After compound 48/80
ASA-sensitive asthmatics	23	42.3	165 SD ± 69	237 SD ± 147	36.5 SD ± 11	46.1 SD ± 12
Non-sensitive asthmatics	33	39.2	199 SD ± 70	254 SD ± 145	41.0 SD ± 10.5	45.8 SD ± 11
			<i>P</i> > 0.1	<i>P</i> > 0.1	<i>P</i> > 0.1	<i>P</i> > 0.1

Table 2

Characteristic of groups, mean ASA dose changes in FEV₁ after ASA ingestion

	Patients <i>n</i>	Age in years (mean - range)	ASA dose mg (range)	Change of % FEV ₁ after ASA challenge (fall from pre-ASA values)
ASA-sensitive asthmatics	16	39.4 (22-57)	154.2 (20-600)	34 range 20-54
Non-sensitive asthmatics	11	43.1	150	no change
Non-sensitive asthmatics	15	38.8 (20-59)	600	no change

Table 3

Influence of ASA on weal and flare responses to intradermal histamine and compound 48/80 (read in 15 min) in ASA-sensitive and ASA-non-sensitive asthmatics

	Skin response to i.d. compound 48/80				Skin response to i.d. histamine			
	Area of weal in mm ²		Diameter of flare in mm		Area of weal in mm ²		Area of flare in mm	
	Before ASA	After ASA	Before ASA	After ASA	Before ASA	After ASA	Before ASA	After ASA
ASA-sensitive asthmatics mean dose 150 mg, <i>n</i> = 16	209 ± 101	301* ± 149	46.2 ± 18	47.5 ± 12	160 ± 103	150 ± 55.7	35.6 ± 9.8	36.5 ± 14
Non-sensitive asthmatics tested with 150 mg ASA <i>n</i> = 11	252 ± 84	251 ± 101	46 ± 11	40 ± 14	185 ± 53.8	174 ± 65.7	38.6 ± 10.5	41 ± 12
Non-sensitive asthmatics tested with 600 mg ASA <i>n</i> = 15	297 ± 129	235 ± 114	49 ± 13	43* ± 10.4	214 ± 89	179 ± 67.5	42.3 ± 8.4	42 ± 11.7

All values given as mean ± SD.

* Differences significant $P < 0.05$.

ASA effect on skin reactions to histamine

There were no significant differences between mean area of weals and mean diameters of flares after histamine before and after oral aspirin in the group of ASA-sensitive asthmatics and in the group of non-sensitive asthmatics tested with 150 mg ASA ($P > 0.05$) (Table 3). 600 mg ASA given to non-sensitive asthmatics inhibited weal but not flare response to histamine (injected 100 min after) as compared with predrug values but was without statistical significance ($P > 0.05$) (Table 3).

ASA effect on skin reactions to compound 48/80

ASA significantly increases weal response to compound 48/80 injected during duration of post ASA bronchoconstriction in ASA-sensitive asthmatics ($P > 0.05$) (Table 3).

In the group of non-sensitive asthmatics 150 mg ASA did not influence the weal and flare response to compound 48/80 ($P > 0.05$). 150 mg ASA did not influence the degree of the flare response after compound 48/80, in either the group of ASA-sensitive asthmatics or the non-sensitive asthmatic subjects ($P > 0.05$). The dose

600 mg, however, significantly diminished the flare ($P < 0.05$) but not the weal response to compound 48/80 in non-sensitive asthmatics. Generally, after 600 mg ASA there was a tendency (except for the flare after histamine) towards diminished response to both injected substances (Table 3).

DISCUSSION

The study showed similar skin reactivity to histamine and compound 48/80 in ASA sensitive and non-sensitive asthmatics. The differences in skin reactions between both groups were revealed only after ASA administration. In ASA-sensitive asthmatics oral administration of this drug significantly increased the weal reaction to compound 48/80.

In healthy persons 150 mg (corresponding to a mean test dose in ASA-sensitive patients) did not change the mean weal response. Since 150 mg ASA does not influence the weal and flare response to exogenous histamine in ASA-sensitive asthmatics it can be concluded that the action of ASA in ASA-sensitive persons concerns mainly mediator release from mast cells rather than induction by histamine of second-

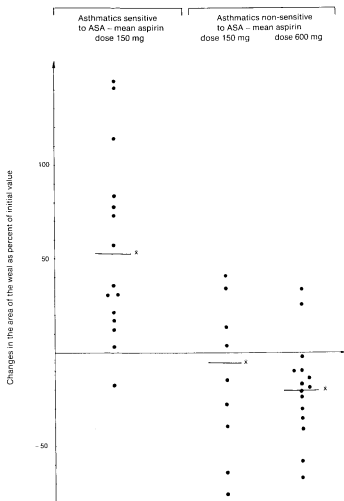


Fig. 1. Influence of oral ASA on weal response to intradermal injection of compound 48/80 in ASA-sensitive and ASA-non-sensitive asthmatics.

any mediators in the adjacent tissue. It is thought that ASA, due to its influence on prostaglandin synthetase, leads to a decrease in prostaglandin E concentration which, in turn enhances mast cell degranulation (4). Another explanation is also possible. The increase of weal after ASA in our experiment is not necessarily connected only with the increased histamine release. The mediator which may also increase the permeability of vessels is slow reacting substance of anaphylaxis (SRS-A) (13). It is known that after cyclooxygenase inhibition by ASA more arachidonic acid is available for

SRS-A synthesis on the lipooxygenase pathway (6), thus enhancing the formation of SRS-A. It is assumed, that SRS-A in ASA-sensitive asthmatics after ingestion of ASA may be the main mediator responsible for symptoms of intolerance. It is also known that SRS-A increases permeability of the vessels to a greater extent than histamine (13). Because in non-sensitive asthmatics, ASA in a higher dose diminished skin response to compound 48/80 one can assume that prostaglandins are involved.

In the groups of ASA-sensitive asthmatics bronchoconstriction is the main symptom of

this sensitivity. In some persons, sensitivity is manifested also as skin symptoms. It seems that our study, designed to elicit mast cell degranulation in the skin of ASA-sensitive asthmatics, simulates in some way phenomena which occur in the bronchi of these persons after ASA challenge. In our previous studies, we suggested that sensitivity to ASA in the bronchi was demonstrated only when bronchial hyperreactivity had developed due to allergy or infection (12). From the presented material one may judge that in ASA-sensitive asthmatics ASA may increase mediator release also in the skin, but only after this release had been originated by some other factors. In our study compound 48/80 was such a factor.

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