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The Effect of Aspirin during Aspirin "Desensitisation" on Compound 48/80 and Histamine-Induced Skin Responses in Aspirin-Sensitive Asthmatics

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In a group of aspirin-sensitive asthmatics we studied skin weal and flare responses to intradermal injections of compound 48/80 and histamine during oral aspirin (ASA) provocation and after ASA "desensitisation". During provocation (bronchospasm accompanied by naso-ocular symptoms) the mean weal area after compound 48/80 increased to about 42.4% ($P < 0.05$). Neither the threshold (provocative) doses of ASA nor 600 mg ASA, when given after ASA-desensitisation, significantly influenced the weal reactions to compound 48/80 (mean changes of area were −1.8% and −16.5% respectively). Aspirin did not change flare reactions to compound 48/80 and weal and flare reactions to histamine on any of the three study occasions. Initial (pre-aspirin) weal reactions to compound 48/80 after desensitisation to the threshold ASA doses were significantly reduced, but after desensitisation to 600 mg ASA were significantly increased as compared with the reactions before. These data suggest that ASA-"desensitisation" may influence the skin reactivity to non-specific mast cell degranulating stimulus in ASA-sensitive asthmatics.

Key words: aspirin intolerance; asthma with aspirin sensitivity; "desensitisation" to aspirin; skin responses to compound 48/80 and histamine.

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Aspirin (acetylsalicylic acid:ASA) and other nonsteroidal anti-inflammatory drugs (NSAID) induce bronchoconstriction in a well-defined subgroup of asthmatics who also suffer from chronic rhinosinusitis and nasal polyps (6, 12). Extrabronchial symptoms of ASA-sensitivity in asthmatics include rhinorrhea, lacrimation, flushing, but rarely urticaria. So far, there has been no evidence that ASA-sensitivity has an immunological background and alternative non-immunological hypotheses remain unproved (13, 22). A prevailing pathogenic hypothesis is that intolerance to ASA and other NSAID depends on the ability of these drugs to inhibit the cyclooxygenase pathway of arachidonic acid (AA) metabolism (16, 17). It remains uncertain whether NSAID provoke an adverse reaction by inducing prostaglandins imbalance, or by activating an alternative lipoxygenase pathway of AA metabolism in the respiratory tract of sensitive asthmatics.

Several studies have confirmed the observation of Widal et al. (23) that "desensitisation" to aspirin can easily be achieved by administering increasing doses of ASA (2, 7, 11, 25). It has also been shown that after "desensitisation" aspirin may improve the clinical course of asthma in some patients (3, 8, 15). In our previous study of ASA-sensitive asthmatics we demonstrated that provocative doses of ASA intensified the weal skin response to compound 48/80 (mast cell degranulator) (18). The purpose of this study was to determine 1) the influence of different ASA doses during the course of "de-

sensitisation" on skin responses to compound 48/80 and histamine, and 2) the influence of ASA "desensitisation" on skin reactivity to both agents.

MATERIAL AND METHODS

Subjects

The study comprised 17 ASA-sensitive asthmatics (8 women and 9 men) ranging in age from 20 to 54 years. Nine of them were considered to be atopics. Aspirin thresholds had been established by double-blind, placebo controlled oral challenge 2–4 weeks before the study and ranged from 20 to 600 mg of ASA (mean 192 mg). The procedure of ASA "desensitisation" has been previously described (17). The previously established threshold dose of aspirin to elicit bronchial reaction was given and then repeated at 24-h intervals until well tolerated. ASA doses were then doubled until good tolerance of 600 mg was achieved. Spirometry was done every 30 min for 3 h after each dose of ASA. Bronchodilators had been discontinued for 8 h, steroids and anti-histaminics for at least 72 h before skin testing.

Skin tests

Intradermal injections of 0.1 ml compound 48/80 (1 mg per ml; Sigma Co.), and histamine phosphate (0.1 mg histamine base per ml; Sigma Co.) were given on the flexor surface of the upper arm using one skin site per test throughout to avoid a local refractory state. Weal reactions were measured after 15 min on two perpendicular axes (a and b) and the areas (S) were calculated according to the formula

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

Flare diameters were measured only at right angles to the longitudinal axis of the forearm. All tests were performed and measured by a nurse who had practiced and standardized the experimental procedures during previous investigations (18) and was not aware of the aim of the study.

The results were evaluated by Student's t paired test.

Study design

Skin tests were performed in parallel with aspirin "desensitisation" on three separate occasions A, B and C. On each occasion the tests were performed before and after ASA administration.

Test day A. In 17 patients the initial weal and flare reactions to compound 48/80 and histamine were measured on the left forearm 30 min before administering the threshold dose. When bronchial reaction to ASA occurred, i.e. $>20\%$ fall in FEV_1, skin tests were repeated in an identical manner on the right forearm.

Test day B. In 12 patients, the day after tolerance of threshold dose was achieved (usually on day 3–4 of the trial), skin tests were performed before ASA administration and repeated on the other forearm after ingestion of threshold dose as on day A.

Test day C. The above procedure of skin testing was repeated in 12 patients the day after achieving tolerance of 600 mg ASA, before and after ingestion of that dose. This was between day 6 and 11 after the initial challenge with aspirin.

RESULTS

All 17 patients exhibited bronchial reaction ($>$ 20% fall in FEV_1) after threshold dose of ASA; 14 also had naso-ocular symptoms and five patients facial flushing. In the following days all patients were "desensitised" to 600 mg ASA.

Effect of single ASA dose on skin responses to compound 48/80 and histamine

Test day A. In the whole group the mean time between aspirin ingestion and skin retesting was 117 min (range 70–150 min). There was a significant increase in the mean weal area after compound 48/80 given during ASA-induced

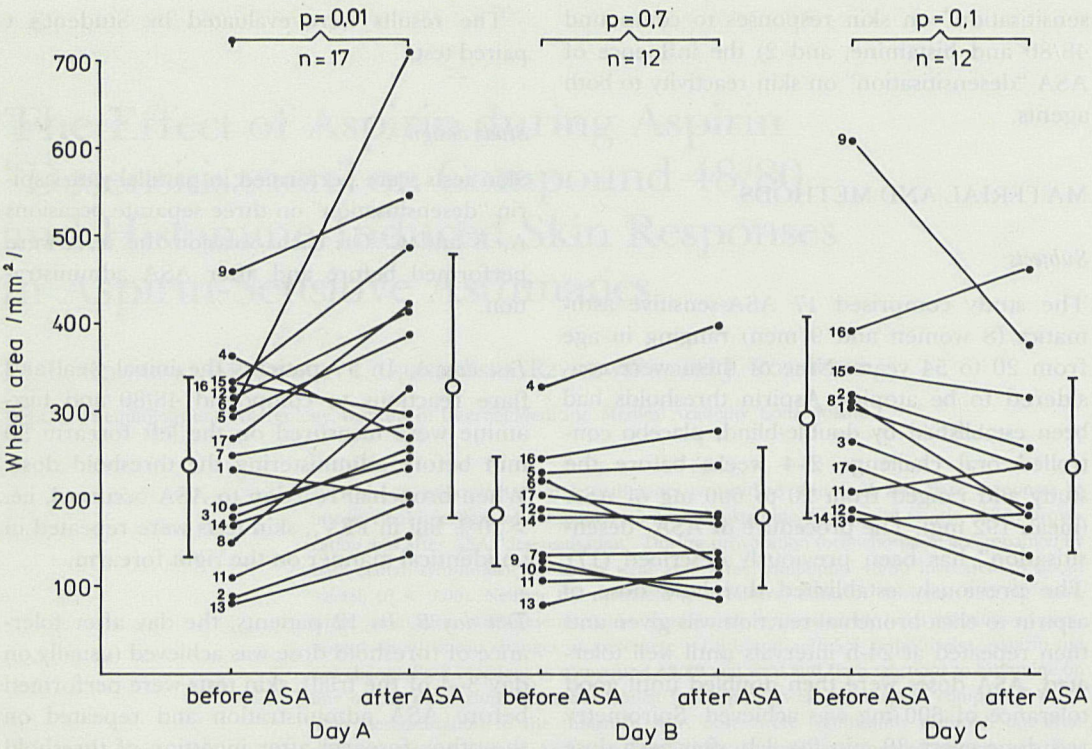

Fig. 1. Influence of threshold ASA doses on provocation (day A): threshold ASA doses after "desensitisation" (day B) and 600 mg ASA after "desensitisation" (day C) on weal response to compound 48/80 in ASA-sensitive asthmatics.
Open circles = group means; vertical bars = SD of group means.

Table 1

Influence of ASA on flare response to compound 48/80 and weal and flare response to histamine on three different occasions (days A, B and C) during "desensitisation"

	Test day A (n = 17)		Test day B (n = 12)		Test day C (n = 12)	
	Before ASA	After ASA	Before ASA	After ASA	Before ASA	After ASA
Flare diameter (mm) after compound 48/80	47 ± 16	50 ± 13	48 ± 11	45 ± 12	48 ± 9	43 ± 13
Weal area (mm^2) after histamine	158 ± 74	160 ± 50	184 ± 97	147 ± 63	155 ± 68	154 ± 76
Flare diameter (mm) after histamine	37 ± 12	35 ± 11	36 ± 17	37 ± 18	35 ± 7	37 ± 12

All values given as mean ± SD.
Data in parentheses indicate the number of patients.

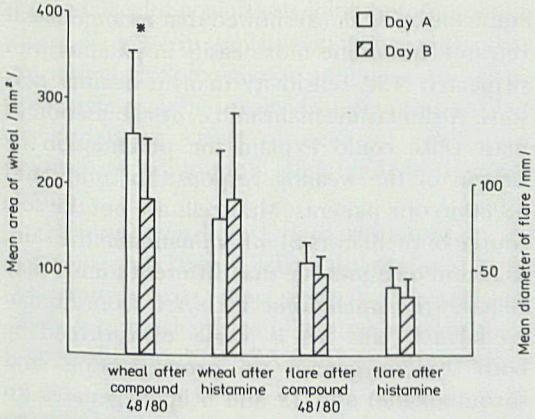

Fig. 2. Comparison of mean initial (pre-aspirin) weal and flare responses to compound 48/80 and histamine before "desensitisation" to ASA (day A) and the day after "desensitisation" to threshold ASA doses (day B) in 12 ASA-sensitive asthmatics.

Vertical bars = SD of means. * Differences significant $P < 0.05$.

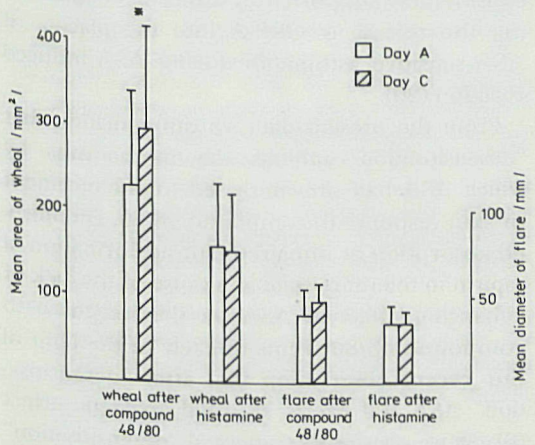

Fig. 3. Comparison of mean initial (pre-aspirin) weal and flare responses to compound 48/80 and histamine before "desensitisation" to ASA (day A) and the day after "desensitisation" to 600 mg ASA (day C) in 12 ASA-sensitive asthmatics.

Vertical bars = SD of means. * Differences significant $P < 0.05$.

reaction as compared with pre-aspirin values on that day (control: 244 ± 101 mm² and aspirin: 331 ± 128 mm²) (Fig. 1).

Test day B. The threshold dose of ASA given after "desensitisation" did not influence the mean weal reaction to compound 48/80 (control: 186 ± 66 mm²; aspirin: 182 ± 89 mm²).

Test day C. There was a tendency to a decrease in the mean weal reaction to compound 48/80 with 600 mg aspirin given orally in tolerance state (control: 296 ± 115; aspirin: 242 ± 98 mm²), but the mean change did not reach statistical significance. Aspirin did not alter the mean flare reactions to compound 48/80 and the weal and flare reactions to histamine on any of the three occasions (Table 1).

Initial (pre-aspirin) skin responses to compound 48/80 and histamine during "desensitisation"

In 12 patients we could compare the initial (pre-aspirin) weal and flare reactions to compound 48/80 and histamine on day B versus day A, and in 12 patients on day C versus day A. There was a significant decrease in the mean initial wheal reaction to compound 48/80 on day B compared with day A ($P < 0.05$) (Fig. 2). The mean wheal reaction to compound 48/80 on day C was significantly increased compared with the response on day A ($P < 0.05$) (Fig. 3). Neither the flare reactions to compound 48/80 nor the weal and flare reactions to histamine differed significantly in that period.

DISCUSSION

The present study demonstrates that "desensitisation" to the adverse effects of aspirin influences the skin response to compound 48/80 (a mast cell degranulator) in ASA-sensitive asthmatics. The skin response to compound 48/80 was augmented during adverse reactions to ASA, but not when the threshold dose of aspirin was repeated in refractory state (after "desensitisation"). After administration of 600 mg ASA the wheals even tended to diminish in size. In this case each patient served as his own control and the changes in weal response to compound 48/80 under aspirin were apparent, both by comparing mean values and by analysis of individual skin reactions. It is more difficult to interprete the fluctuation of initial pre-aspi-

rin weal responses to compound 48/80 during "desensitisation" because, as shown in Fig. 1, only seven out of 17 patients were tested on each of the three occasions (days A, B and C), and the number of patients was too small for statistical analysis. Finally, in each of the two overlapping subgroups of patients (12 in each) we could compare the initial skin responses measured twice: day A versus day B in one subgroup and day A versus day C in the other. As shown in Fig. 2, the mean initial pre-aspirin weal responses to compound 48/80 were diminished the day after a tolerance of threshold ASA dose had been achieved (day B vs. day A). The assumption that it was due to local refractory period (5) can be ruled out, as we were careful to change the injection sites during the study. In patients with cold urticaria Bentley-Phillips et al. (1) have shown diminished wealing response to compound 48/80 after locally induced tolerance to cold, and attributed the phenomenon to histamine depletion of skin during the "desensitisation" procedure. However, a similar mechanism could not be operating in our patients as the majority of them did not reveal any noticeable adverse skin symptoms during ASA-induced bronchoconstriction and during further "desensitisation". The day after tolerance of 600 mg ASA had been achieved (day C) the mean initial (pre-aspirin) weal responses to compound 48/80 were significantly increased as compared with reactions on day A. This proves that, at least in that subgroup of patients, mediators were permanently present in skin mast cells after "desensitisation" and this quantity was not smaller than before desensitisation.

This study confirmed our previous observation of an augmented wealing response to histamine liberators during ASA-induced bronchoconstriction in sensitive asthmatics (18). Since aspirin did not influence the weal and flare response to histamine in that time, it was conceivable that the drug influenced production and/or release of mediators from skin mast cells, rather than affected skin vessel permeability to those mediators. Cyclooxygenase inhibitors (e.g. aspirin or indomethacin) may increase histamine release from human leukocytes (10, 24), and Conroy et al. (4) showed that indomethacin released histamine more easily in patients with suspected ASA-sensitivity than in healthy persons. A similar mechanism, i.e. destabilisation of mast cells, could explain the potentiation by aspirin of the wealing response to compound 48/80 in our patients. Mast cells are not the sole source of mediators of inflammation in the skin, as recent data indicate that different stimuli may release free arachidonic acid (AA) from human epidermal cells. AA is locally transformed by both cyclooxygenase (to prostaglandins and thromboxane) and 12 and 5 lipoxygenases (to hydroxyeicosatetraenoic acids and leukotrienes (21)). As we suggested previously, the increased wealing response to compound 48/80 during ASA-induced bronchoconstriction might result from enhancement by aspirin of SRS-A (leukotrienes) synthesis on lipoxygenase pathway of AA metabolism (18). This assumption has been considerably supported by a recent study showing the release of SRS-A into the plasma of ASA-sensitive asthmatics during ASA-induced reaction (20).

From the present data we can conclude that "desensitisation" inhibits the mechanisms by which ASA had previously led to enhancement of skin response to compound 48/80. Diminished absorption or impaired biotransformation of aspirin in tolerance state as a cause of the lack of enhancing effect of ASA on skin response to compound 48/80 seems unlikely in the light of our recent observation that after "desensitisation" ASA still exerts its usual analgetic effect (8). As we previously suggested "desensitisation" to ASA may result from ability of ASA to inhibit, under certain conditions, not only cyclooxygenase but also lipoxygenase pathway of AA metabolism (9, 19). On the other hand, the following data support our assumption (7) that "desensitisation" to ASA is related to persistent cyclooxygenase inhibtion by the drug:ASA-induced refractory period includes also tolerance to other cyclooxygenase inhibitors which previously showed cross-sensitivity with aspirin (7, 11); furthermore, the length of the refractory period after aspirin "desensitisation" (3–7 days) is apparently similar to the duration of serum thromboxan B_2 and prostaglandins E_1,

E_2 and F_2 alpha synthesis inhibition by a single dose of ASA in sensitive patients (14). Thus persistent cyclooxygenase inhibition in refractory state may be involved in the observed lack of enhancing effect of ASA on wealing response to compound 48/80 after "desensitisation".

Although weal and flare responses in the skin may not strictly reflect the situation in the respiratory tract, they seem to give some insight into mechanisms of aspirin sensitivity and "desensitisation" in ASA-sensitive asthmatics.

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