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Tolerance to acetylsalicylic acid (ASA) induced in ASA-sensitive asthmatics does not depend on initial adverse reaction

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A state of tolerance to aspirin (ASA) was induced in 10 aspirin-sensitive patients by daily administration of incremental doses of ASA. No adverse reactions were reported. The initial dose (from 5 to 60 mg) was gradually increased each day up to 300 mg and then doubled. 50 mg indomethacin given the day after administration of 600 mg ASA did not elicit any symptom of intolerance. The authors discuss a possible mechanism of tolerance to aspirin in ASA-sensitive asthmatics after ASA administration, suggesting that it might be connected either with inhibition of the lipooxygenetic pathway of arachidonic acid metabolism or with blockade of the cyclooxygenase supplementary binding site by salicylic acid, a product of acetylsalicylic acid hydrolysis. This would prevent aspirin from binding with the catalytic cyclooxygenase site.

Key words: aspirin-sensitive asthma; aspirin tolerance; arachidonic acid metabolism; cyclooxygenase.

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CLINICAL ASPECTS

The authors describe a method of eliciting aspirin sensitivity by daily administration of gradually increasing aspirin doses, starting with subthreshold doses. This method makes it possible to induce tolerance to aspirin without provoking adverse reactions.

Aspirin-sensitive asthma is a serious clinical problem, frequently involving dramatic exacerbations and sometimes even danger of death after accidental ingestion of aspirin (acetylsalicylic acid-ASA) or other nonsteroidal anti-inflammatory drugs (NSAID) (3, 15). Exacerbation may also occur in aspirin-sensitive asthmatics after intake of drugs or food products containing tartrazine (1). Aspirin-sensitive asthma is not infrequent and occurs in 4–20% of asthmatic patients (15). Some data indicate a relationship between inhibition of prostaglandin biosynthesis by NSAIDs and their potential for eliciting dyspnea attacks in sensitive asthmatics (14). Widal et al. already in 1922 and later Zeiss & Lockey in 1976 found it possible to elicit tolerance to NSAIDs in sensitive patients (17, 18). Recently, the study of Stevenson et al. (13) and our own investigation (3) have demonstrated a possibility of eliciting and maintaining tolerance to ASA in a large group of aspirin-sensitive asthmatics by administration of aspirin at appropriate intervals (6, 13). In some of these patients aspirin given after desensitisation had an undoubtedly beneficial effect on the clinical course of their asthma. However, in all the studies performed so far, the tolerance state was preceded by dyspnea and varying intensity of extrabronchial symptoms of sensitivity (6, 13). On the basis of this observation Stevenson et al. hypothesised that the tolerance state to

NSAIDs is related to the initial sensitivity reaction and may depend on the depletion of preformed mediators from mast cells (13). From our previous observations one may judge that the smaller the aspirin dose, the weaker the sensitivity symptoms and that it is possible to induce tolerance after eliciting only very slight sensitivity reactions (6). It seemed to us, therefore, that we might obtain aspirin tolerance preceded by weak sensitivity symptoms or none at all, if we administered subthreshold, gradually increasing aspirin doses to sensitive asthmatics. The procedure and results are reported.

MATERIAL AND METHODS

Aspirin tolerance was elicited in 10 aspirin-sensitive asthmatics, all of whom were in remission and had normal ventilatory parameters, i.e. vital capacity (VC) and forced expiratory volume in 1st s (FEV_1) measured with a Pneumoscreen (Jaeger). Firstly, the threshold aspirin dose, i.e. the smallest ASA dose inducing at least 20% fall in FEV_1, was established (3) according to the method described previously. After at least 2 weeks, a 2-4 times smaller dose of ASA was given and if this dose elicited neither a sensitivity reaction nor a decrease in ventilatory parameters within 3 h it was regarded as subthreshold dose. At 24-h intervals, consecutive ASA doses were administered, increasing by 20 mg up to a good tolerance dose of 300 mg. When 300 mg ASA had been well tolerated, the double ASA dose and 50 mg indomethacin dose were given on two subsequent days. In one patient (J.T.) with a very low ASA threshold (20 mg), the initial dose of 5 mg was increased by 5 mg every 24 h, until a good tolerance of 20 mg was achieved, after which the procedure was the same as in the remaining patients. Ventilatory parameters (VC and FEV_1) were measured before the trial and then for 3 h at 30-min intervals after each ASA dose, using a Pneumoscreen. The patients monitored symptoms, such as dyspnea and extrabronchial sensitivity, after leaving the clinic. During this study, as when establishing

Table 1

Procedure by which tolerance to aspirin (ASA) was elicited in 10 asthmatics sensitive to ASA

Patient	Age	Sex	Threshold dose of ASA	Subthreshold dose of ASA	Symptoms of intolerance after threshold dose of ASA	Intolerance symptoms during inducing of tolerance state	Tolerance of 600 mg ASA or 50 mg indomethacin
C.R.	47	♀	100	40	dyspnea, watery rhinorrhea	none	good
J.T.	48	♀	20	5	dyspnea, watery rhinorrhea	none	good
J.M.	50	♀	60	20	dyspnea	none	good
K.P.	46	♀	160	60	dyspnea, watery rhinorrhea	none	good
W.J.	25	♂	60	20	dyspnea, watery rhinorrhea	none	good
J.K.	57	♂	120	60	dyspnea	none	good
B.L.	54	♀	80	40	dyspnea, watery rhinorrhea	none	good
L.P.	30	♂	60	20	dyspnea	none	good
W.J.	35	♀	80	20	dyspnea	none	good
G.S.	52	♂	100	40	dyspnea, watery rhinorrhea	none	good

the threshold provocation ASA dose, no disodium cromoglycate, antihistamine drugs, or corticosteroids were given. Bronchodilatating drugs were not applied until 8 h before examination.

RESULTS

By administering a subthreshold ASA dose followed by increasing doses of 20 mg every 24 h, a good tolerance of 300 mg ASA was achieved in all patients. After the threshold provocation dose, all tested patients had dyspnea as well as a 30–60 % fall in FEV_1, and six of them had watery rhinorrhea. None of the examined patients experienced dyspnea or extrabronchial sensitivity symptoms during the procedure of developing tolerance, and none had a significant FEV_1 fall. The doubled ASA dose, i.e. 600 mg and 50 mg indomethacin administered the next day, were also well tolerated (no fall in FEV_1 20 %, no extrabronchial symptoms (Table 1)).

DISCUSSION

In all patients good tolerance of 600 mg aspirin was achieved by giving a subthreshold aspirin dose and increasing it gradually every day. With this procedure none of the patients suffered dyspnea or extrabronchial adverse reactions to ASA. Thus it seems unlikely that tolerance to nonsteroidal anti-inflammatory drugs depends on depletion of preformed mediators from mast cells. We have recently suggested that the aspirin tolerance mechanism is connected with cyclooxygenase inhibition (6). Aspirin, however, if given in high enough doses, also inhibits the lipooxygenetic pathway of arachidonic acid metabolism. Paajanen et al. showed that in hamster isolated lungs aspirin inhibits not only arachidonic acid metabolism via cyclooxygenase but also via lipooxygenase (8). This has also been confirmed in rat studies (4, 5) where reduced migration of neutrophilic leucocytes to the inflammatory focus was observed after high doses of aspirin, indomethacin or other nonsteroidal anti-inflammatory drugs. This should mainly be ascribed to inhibition of monohydroxyeicosatetraenoic acid (HETE) and leukotrienes formation. HETEs and leukotrienes are known to be the most potent chemotactic factors for leukocytes (12). Recently, Leftwich et al. (7) showed more than 50 % decrease in leukotriene production in mononuclear, human leukocytes from healthy subjects after ingestion of 650 mg ASA. It is believed that in aspirin-sensitive asthmatics small doses of aspirin after cyclooxygenase inhibition enhance arachidonic acid metabolism on lipooxygenetic pathway, leading to the formation of large amounts of leukotrienes (15). It might therefore be suggested that in ASA-sensitive asthmatics in the ASA tolerance state higher doses of aspirin not only inhibit cyclooxygenase but also the metabolism of arachidonic acid via the lipooxygenetic pathway.

However, another explanation of the observed results is also possible. It has been shown that cyclooxygenase possesses two different sites which may be affected by NSAIDs: the catalytic center, via which the enzyme is irreversibly inactivated by aspirin, and the supplementary binding site, the binding with which by some agents, e.g. sodium salicylate, prevents aspirin from reaching the catalytic center (1, 11). This interaction between NaSal and aspirin concerns asthmatics sensitive to ASA as well. We have shown that administration of sodium salicylate prior to the administration of aspirin in ASA-sensitive asthmatics protects most of them from bronchoconstriction elicited by aspirin (16). It is known that aspirin mostly hydrolyses to salicylic acid in the organism (8). It is possible that in our study the aspirin doses, which were small enough not to elicit sensitivity symptoms, were the source of salicylic acid through hydrolysis. In turn, by binding with cyclooxygenase supplementary binding site, salicylic acid prevented consecutive aspirin molecules from reaching the catalytic site and inducing sensitivity symptoms. The described phenomenon may be the basic mechanism of the development of tolerance to aspirin.

The same mechanism may underlie the observed good tolerance of indomethacin after the development of ASA tolerance in our ASA-sensitive asthmatics and those reported by Pleskov (10).

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