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Bronchial Response to Nonsteroidal Anti-Inflammatory Drugs in Asthmatic Patients

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Nonsteroidal anti-inflammatory drugs (NSAIDs) cannot, as a rule, be considered bronchoactive agents. There are, however, several exceptions to this statement that should be considered. We examine these under the following topics: antireactive activity, bronchodilator activity, and bronchoconstrictor activity. Also considered are late reactions to NSAIDs and immediate reactions to pyrazolone drugs.

Antireactive Activity

NSAIDs do not affect the immediate bronchial response to exercise and allergens in asthmatics [1–3]. They can inhibit the late allergic response [4], but this finding has to be confirmed. In a previous open study [5] we found that 50 mg of aspirin (ASA) given by inhalation (aerosol of a solution of lysine-acetylsalicylate: L-ASA) 1 h prior to the challenge did not prevent the bronchoconstriction induced by an ultrasonic mist of distilled water (H₂O) in 5 asthmatic patients. More recently, however, we have demonstrated that, in some experimental conditions, oral ASA can afford a rather good protection against this agent.

Two well-matched groups of adult asymptomatic patients, who needed only irregular medication (β_2 -stimulants by inhalation) to control their asthma, were studied. In the first study, 12 patients received 1-g dose per os of ASA 1 h prior to the challenge; in the second study, 10 patients received seven 1-g doses per os of ASA (1 g every 12 h), with the last dose 1 h prior to the challenge. Both studies were double-blind and placebo controlled. The time interval between the two challenges was 2–3 days in the

Table I. Effect of premedication with ASA (1 g p.o., 1 h prior to challenge) on bronchial obstruction (sRaw, cm H₂O · s) induced by an ultrasonic mist of H₂O in a group of 12 asthmatic patients.

Treatments		Control	Control	Times of exposure to H ₂ O mist		
				30 s	60 s	120 s
Placebo	$\bar{x}$	9.35	9.16	15.47	25.12	46.39
	SEM	1.07	1.17	2.33	3.30	5.94
ASA (1 g)	$\bar{x}$	9.12	7.75	12.45	19.23	33.79
	SEM	1.41	0.67	1.22	1.84	3.43
t		NS	NS	NS	NS	S*

S* = Significant at the 1% level; NS = not significant.

Table II. Effect of premedication with ASA (7 g p.o.: 1 g every 12 h, last dose 1 h prior to challenge) on bronchial obstruction (sRaw, cm H₂O · s) induced by ultrasonic mist of H₂O in a group of 10 asthmatic patients.

Treatments		Control	Control	Times of exposure to H ₂ O mist		
				30 s	60 s	120 s
Placebo	$\bar{x}$	7.35	7.33	13.16	21.31	42.41
	SEM	1.11	0.81	2.60	4.26	6.77
ASA (7 g)	$\bar{x}$	7.63	7.01	10.67	14.69	24.76
	SEM	0.48	0.63	1.40	2.44	4.51
t		NS	NS	NS	S*	S*

S* = Significant at the 1% level; NS = not significant.

first study and 7 days in the second study. The ultrasonic mist was produced by a mistogen apparatus (model EN 143) adjusted to deliver 2 ml/min. For each challenge three exposures of 30.60 and 120 s were given at 4-min intervals. Specific airway resistance (sRaw) was measured under basal conditions (immediately prior to treatment and challenge) and after each exposure according to a method described in detail elsewhere [6].

The average results of the two studies are shown in tables I and II. 1 g ASA treatment accentuated the bronchial response to H₂O in 1 subject,

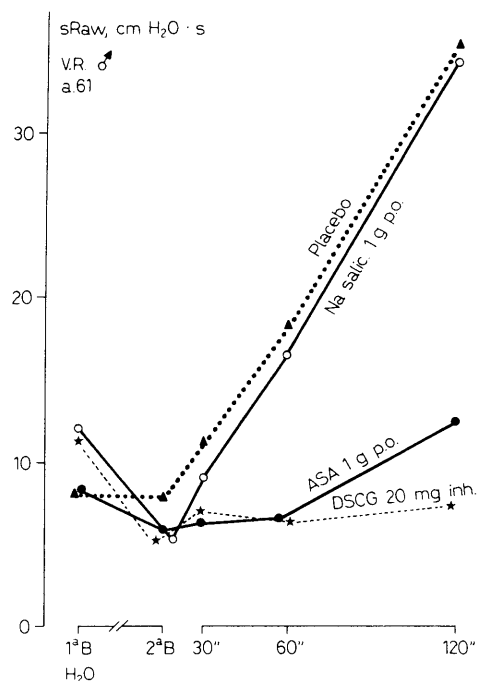


Fig. 1. Effect of aspirin (ASA) (1 g p.o., 1 h prior to challenge), sodium salicylate (1 g p.o., 1 h prior to challenge), and DSCG (20 mg by inhalation 30 min prior to challenge) on the bronchoconstriction induced by an ultrasonic mist of distilled water in an intrinsic asthmatic patient.

was ineffective in 6 and afforded a fairly good (in 3) or good (in 2) protection in the remaining subjects. The mean (SEM) % protective effect (sRaw increase after placebo minus sRaw increase after ASA divided by sRaw increase after placebo; in case of negative results, the protective effect was calculated by interchanging the placebo with ASA) was 22.2 ± 13.5 , which, in clinical terms, is negligible. 7 g ASA treatment accentuated H₂O bronchospasm in 1 subject, was ineffective in 2, and afforded a moderate (in 1), fairly good (in 4), or very good (in 3) protection in the remaining subjects. The mean (SEM) % protective effect was 42.5 ± 12.4 , which becomes 51.5 ± 9.0 if the negative result is discarded. This protection is similar in degree to that observed by us in another study [6] after two puffs (200 µg 2 h prior to the challenge) of salbutamol.

The mechanism of the protective effect remains to be established. In 2 patients who were well protected by ASA (1 g p.o.), sodium salicylate was ineffective, suggesting that the inhibition of prostaglandin synthesis could be responsible for the protection. Figure 1 shows 1 of these cases. But, in another patient, seven 1-g doses per os of sodium salicylate afforded a fairly good protection, although lower than that given by the same dose of ASA. Clearly, more data are needed to answer this question. It is, however, worth remembering that tiaramide, a basic NSAID devoid of any anti-cyclooxygenase activity [8], antagonizes H₂O bronchospasm very well [7].

Bronchodilator Activity

In spite of the fact that many patients claim that NSAIDs relieve their asthma, a real bronchodilation can be demonstrated in only a very small number of them [9, 10]. These true responders probably belong to the same family of asthmatics who are very well protected by NSAIDs against nonspecific stimuli. The time course of the bronchodilation induced by ASA (as intravenous L-ASA) in a typical responder is shown in figure 2. It can also be seen that the bronchodilator effect is markedly reduced by a 7-day treatment with ASA (1 g p.o. b.i.d.). The therapeutic corollary of this finding seems to be that this type of patient can take the best advantage from NSAIDs only if the treatment is discontinuous.

A rather similar loss of sensitivity to NSAIDs after repeated administration was observed by us several years ago [11, 12] and confirmed more recently by others [13] in the opposite and more frequent syndrome which is commonly labelled ASA asthma. This can be a further element in favor of the prostaglandin theory (that the benefit and danger are somehow linked with the removal of a product(s) of arachidonic acid cyclooxygenation from the respiratory tract) put forward by Szczeklik et al. [14] to explain the mechanism of the two specular conditions.

Bronchoconstrictor Activity

Bronchoconstriction in response to NSAIDs occurs rather frequently (8–20%) among adult (particularly female) asthmatics, while it is uncommon in children [15]. In collaboration with the Clinica Pediatrica of the

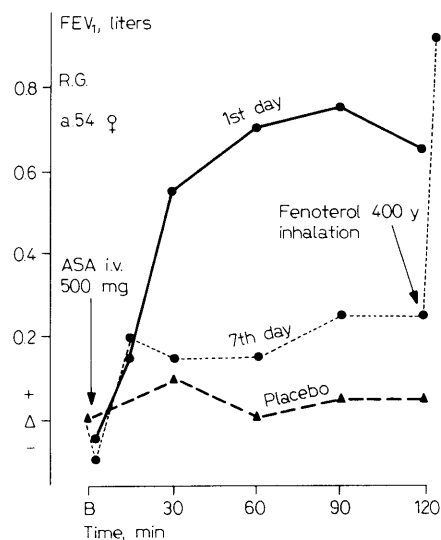


Fig. 2. Bronchodilator effect of aspirin (ASA) (500 mg i.v. as lysine-acetylsalicylate) before and after a 7-day treatment with aspirin (1 g p.o. b.i.d.) in an intrinsic asthmatic patient.

University of Milan, we have challenged 311 asthmatic children with L-ASA with only 4 (1.29%) positive responses.

The inhalation challenge test with the soluble form of ASA (L-ASA) was developed by us about 10 years ago and has been exploited in our laboratory for the detection and study of ASA asthma ever since. We nebulize a freshly prepared solution of L-ASA. In the first exposure 0.65–1.3 mg of ASA are inhaled. If no reaction occurs within 1 h, the dose is increased hourly (by increasing the time of exposure and/or the concentration of the solution) until a positive response is obtained (sRaw increase of at least 80% or FEV₁ decrease of at least 15%) or a top dose of 52 mg is reached [16]. The asthmogenic power of this dose corresponds to 1500–2000 mg ASA ingested. Most ASA-sensitive symptomatic asthmatics respond to 1.3–2.6 mg, which are very low doses considering that only 10% of them enter the bronchial tree.

Classic Obstructive Reaction to NSAIDs

When ASA is inhaled in appropriated doses, the bronchial reaction starts at 15–30 min, peaks after 90–120 min, and lasts 4–5 h. No impor-

tant differences are observed if, instead of ASA, another soluble NSAID is inhaled provided that an equipotent dose is given. Challenge with L-ASA is absolutely safe. The main advantages over the oral challenge are that responses are more prompt, only confined to the respiratory tree (no extrapulmonary symptoms), and always easily controllable. It was when we were checking the reproducibility of L-ASA challenge that we realized for the first time that the daily administration of increasing doses of ASA resulted in a dose-related and temporary loss of sensitivity not only to ASA but also to all cross-reacting NSAIDs [11, 12]. We also realized that it was possible to desensitize only the bronchial tree (oral inhalation) preserving the nasal reactivity or vice versa (nasal drops). This possibility should be kept in mind whenever ASA maintenance treatment in ASA-sensitive patients is planned in order to improve their asthma or rhinitis [17]. At least, if no benefit is obtained, extra-respiratory side-effects (mainly gastrointestinal) will be avoided.

As with many other NSAIDs, tartrazine, which does not inhibit cyclooxygenase activity [18, 19], is reported to be asthmogenic in a considerable percentage (from 4 to 50%) of ASA-sensitive patients. We have never been able to observe any true adverse reaction to this yellow azo dye in spite of using very large doses (up to 2000 mg) to challenge 60 ASA-sensitive patients.

Late Obstructive Reaction to a Pro-NSAID

This type of reaction has been observed by us after administration of fenbufen. The late obstructive reaction begins 3 or more h after taking the drug and lasts for several hours (fig. 3). Fenbufen, 3-(4-biphenylcarbonyl)propionic acid, is an orally effective NSAID which is devoid of any anti-PG synthetase activity. However, one of its major metabolites, *p*-biphenylacetic acid, is a potent inhibitor of prostaglandin production [20]. It is likely that this metabolite accounts not only for the anti-inflammatory effects but also for the asthmogenic effect of fenbufen. If this is the case, the reaction should begin when a sufficient concentration of the active metabolite is attained at the bronchial level. With the usual doses of fenbufen, this only happens when patients are very sensitive to ASA. Thus, in spite of the different time course, the mechanism of the obstructive reactions induced by fenbufen and the other NSAIDs seems essentially the same. Also favoring this view is that induced tolerance to fenbufen extends to the other NSAIDs and vice versa (fig. 4).

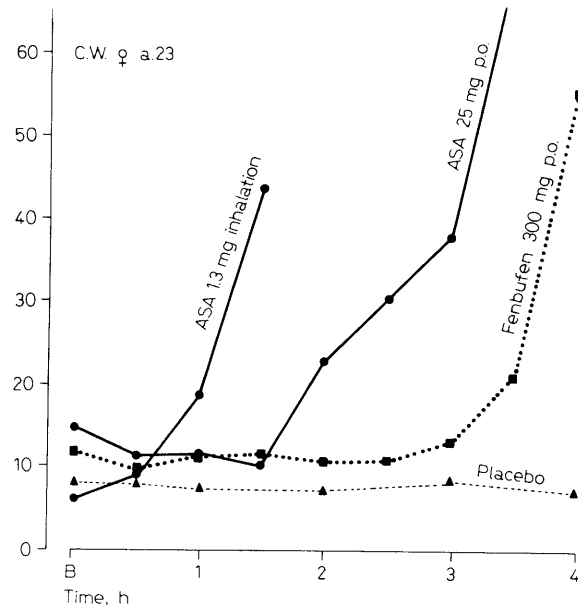


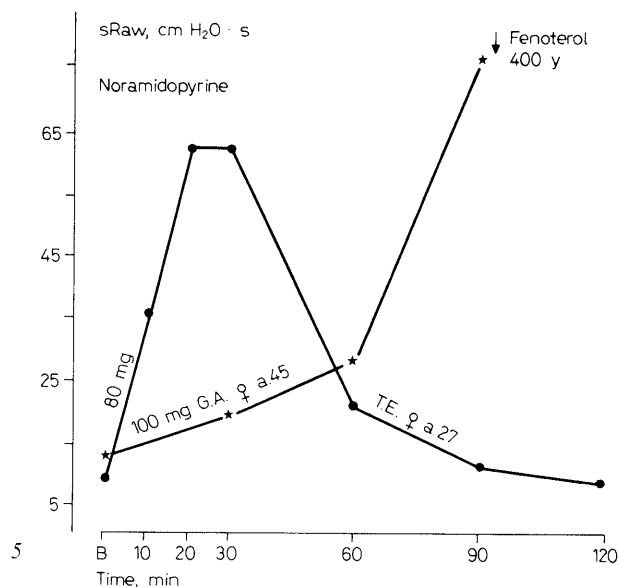
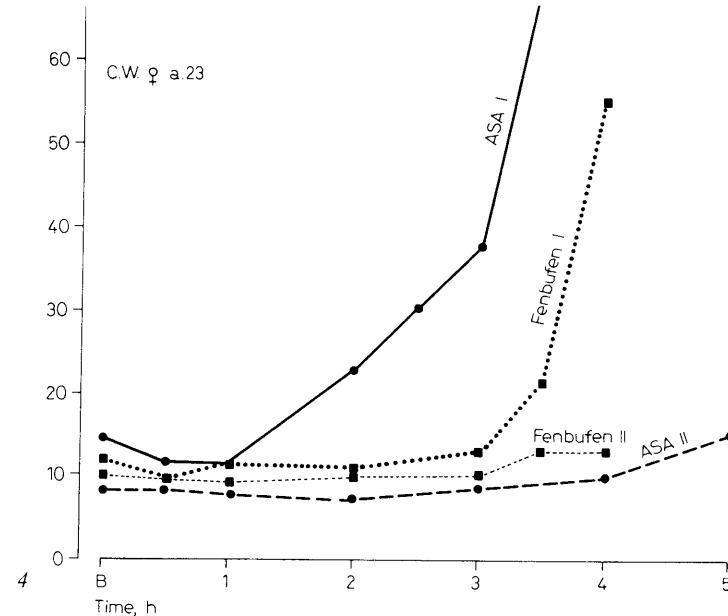
Fig. 3. Bronchial response to aspirin (ASA) (by inhalation and by mouth) and fenbufen in a patient sensitive to NSAIDs.

Immediate and Short-Lasting Obstructive Reaction to Pyrazolone Drugs

We have documented this type of response after noramidopyrine, but it probably also occurs after aminophenazone, since both drugs have been reported to cross-react in inducing anaphylactic shock and/or urticaria [21]. These patients are insensitive to the common asthmogenic NSAIDs. A typical reaction to noramidopyrine is shown in figure 5. For compari-

Fig. 4. Bronchial response to aspirin (ASA) (25 mg p.o.) and fenbufen (300 mg p.o.) before (I) and after (II) a 7-day treatment with fenbufen (300 mg p.o. b.i.d.) in a patient sensitive to NSAIDs.

Fig. 5. Time course of the bronchoconstriction induced by noramidopyrine in a patient sensitive only to pyrazolone drugs. For comparison, the time course of the bronchial response to the same drug in a patient sensitive to all NSAIDs is shown.



son, the reaction to the same drug in an ASA-sensitive patient is also illustrated. The time courses are completely different and, in the first case, the reaction is rather similar to the reaction (IgE-mediated) induced by allergens. Although this does not prove that the pathogenetic mechanisms are identical, the fact that skin tests with these agents were found to be highly positive in patients idiosyncratic to pyrazolone drugs [21] lends support to this view.

Conclusions

NSAIDs can induce both favorable and adverse effects in asthmatics. With respect to the first, we demonstrated that NSAIDs can prevent bronchoconstriction induced by an ultrasonic mist of distilled water. The protection seems to be dose-related, but further studies are needed to clarify this point and to possibly establish if the preventive effect can have any therapeutic implication, at least in the most sensitive patients.

Direct bronchodilation in response to NSAIDs is definitely an unusual event. Its marked attenuation after repeated administration of ASA (observed by us in 1 patient) seems to rule out the possibility of effective long-term treatments with NSAIDs in this type of patient. It will be interesting to see if prevention and bronchodilation are linked in some way.

With regard to the asthmogenic effects of NSAIDs, much attention has recently been devoted to the possibility of inducing and maintaining tolerance to NSAIDs by their repeated administration. We do not believe that this procedure has any specific therapeutic value mainly because intolerance to NSAIDs is not responsible for the asthmatic condition. At the same time, we cannot exclude that some asthmatic patients, regardless of whether they tolerate or do not tolerate NSAIDs, can obtain some benefit from long-term treatment with NSAIDs.

Both immediate and late reactions to NSAIDs deserve some comment. The late reaction seems to strengthen the prostaglandin theory of ASA asthma. However, regardless of any speculation as to theory, the reaction must be kept in mind whenever a pro-NSAID is given in order to be able to properly interpret and treat some otherwise inexplicable asthmatic symptoms.

A similar problem does not arise with pyrazolone drugs because reactions start almost immediately after drug intake. Respiratory symp-

toms are seldom isolated, and are usually accompanied by urticaria and a pronounced fall in blood pressure. In these often dramatic conditions the repeated assessment of ventilatory function is extremely difficult. We found 3 patients in whom the ingestion of a small dose of noramidopyrine induced only bronchial obstruction. This allowed us to study carefully the main features of this peculiar reaction which, in spite of its dramatic beginning, clears up in a short time and responds well to β_2 -stimulants.

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