

Non-Steroid Anti-Inflammatory Drugs in Asthma: Dangerous or Useful Therapy?

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The therapeutic potential of non-steroid anti-inflammatory drugs in clinical asthma is offset by the real possibility of hypersensitivity and induction of severe airways obstruction. The influence of indomethacin on the antigen-induced asthmatic response was tested. Early and delayed asthmatic responses were recorded after antigen challenge in 13 subjects. Indomethacin pretreatment totally or partially inhibited the delayed asthmatic response in 10 of 11 subjects. Inhibition by indomethacin of products of the arachidonic cascade which participate in the pathogenesis of the delayed asthmatic response could explain this phenomenon. A similar therapeutic response was documented without adverse drug reactions when five subjects were restudied after several months. In the same group the early asthmatic response was suppressed in six, enhanced in two and unchanged in four of 12 subjects. This variable response indicates that spasmogenic prostaglandin breakdown products may be important for certain individuals, but are generally of less importance in the early asthmatic response. Clinical trials with indomethacin as a steroid saving agent in allergic asthma appear feasible and can be conducted safely.

Key words: allergic asthmatics; bronchial provocation; delayed asthmatic response; indomethacin; prostaglandin inhibition.

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Non-steroid anti-inflammatory drugs (NSAID) are a well-known cause of severe airways obstruction in individuals with allergic manifestations (19, 27). The safety of these agents for general use in asthmatics may justifiably be questioned, as such untoward reactions may be entirely unpredictable. Enhanced spasmogenic leukotriene production due to inhibition of the cyclooxygenase pathway by the NSAID's has been postulated as a cause of this form of iatrogenic airways obstruction (17). Inhalation challenge studies with leukotriene C₄ and D₄ (LTD₄, LTC₄) have shown how potent the bronchoconstrictor properties of these substances are (14, 29).

The asthmatic response subsequent to inhalation challenge with common inhaled allergens was used as a model to study the relationship between indomethacin and acute asthma. The pattern of asthmatic response subsequent to

antigen challenge has been recorded in 20 individuals who were challenged on several study days, and a consistent response recorded in each individual. This consisted of an early asthmatic response (EAR), delayed asthmatic response (DAR) or both (15). Spasmogens released from mast cells, enhanced airways hyperreactivity to these substances, and neurogenic reflex mechanisms have been held responsible for the EAR (1, 13, 30). The nature of the DAR remains controversial, but the fact that pre-challenge treatment with corticosteroids inhibits the DAR but not the EAR, suggests different mechanisms in the two stages of the reaction (20). It is in relation to the DAR that the chemotactic and vasopermeability properties of breakdown products of the arachidonic cascade, such as thromboxane and leukotrienes, may be relevant (16, 23). Pre-medication with indomethacin prior to inhala-

tion challenge could provide an important insight into the therapeutic and iatrogenic effects, as well as the safety of the group of NSAID's in clinical asthma.

It was therefore the aim of this study to: 1) assess the influence of indomethacin on an experimental model of clinical asthma, 2) gain insight into the role of arachidonic breakdown products in the antigen-induced response, and 3) evaluate the safety and possible therapeutic role of indomethacin in clinical asthma.

METHODS

Subjects

Thirteen asthmatic patients (episodic wheezing with teenage onset) between the ages of 16 and 40 years were studied. One or more positive skin prick reactions to common inhaled allergens were documented in each patient. All were non-smokers. Histories of recurrent chest infections or sputum production were absent in this group and they were otherwise healthy and active people. The subjects studied included four females and nine males. Current therapy prior to the study consisted of prophylactic inhaled beta-stimulants (four subjects), supplementation with an oral theophylline agent (one subject) and inhaled beta-stimulants on demand mostly prior to exercise, in the remaining eight patients. None were on oral or inhaled corticosteroids. Patients ceased taking all anti-asthmatic drugs 12 h prior to the onset of the study. Voluntary consent was obtained from each patient (or their parents) and the study was carried out with the approval of the local Ethics Committee.

Study design

Specific antigens which caused the largest weal on skin prick testing in each individual were employed for bronchial challenge (house dust mite 10, South African grass pollens 2 and cat dander 1 patient). The lung response subsequent to challenge was measured by means of flow volume curves. Patients performed this manoeuvre on a dry seal Collins spirometer

until two identical cues were obtained. The area below the expiratory flow volume curve ($A \dot{V}/V$) was determined electronically and was employed to determine post-challenge lung function change (2). The diurnal pattern of bronchial reactivity to a non-specific challenge of inhaled saline for 5 min was determined at onset of the study. Initial $A \dot{V}/V$ determinations were done at 15-min intervals for the first 1.5 h and thereafter at hourly intervals. The mean $A \dot{V}/V$ was determined for 11 measurements subsequent to saline challenge. One standard deviation was calculated and expressed as a percentage of the mean. The value subsequently obtained was termed significant percentage change (Sig % change) and represented the normal variation in lung function over a 7.5 h period for each individual. EAR's exceeded the significant percentage change at four out of six points in the first hour and a half and DAR's at three out of five points commencing three and a half hours after challenge.

Antigen challenge

Specific antigen solutions and the duration of antigen exposure which induced an adequate bronchial response were determined prior to the onset of the study for each individual. A Devilbiss micronebulizer (model 56) was employed for antigen delivery. Patients inhaled the antigen directly from the nebulizer through a one-way Rubins valve and mouthpiece. All factors pertaining to the amount of antigen delivered were kept constant throughout the study. This included the temperature of the water bath, speed of nebulization, duration of exposure and concentration of freshly prepared antigen solution. The volume of antigen solution delivered by the apparatus amounted to 0.5 ml/min and the exact amount of antigen delivered to each individual could be calculated. Control $A \dot{V}/V$ values, prior to antigen challenge on each study day, varied less than 10% for all patients. Indomethacin, 100 mg/day in four divided doses, or placebo capsules (indomethacin capsule housings filled with glucose) were administered blind to the patients

for 3 days prior to the antigen challenge. Indomethacin and placebo studies were conducted at weekly intervals – with a maximum interval of 3 weeks. The drug response was re-tested in an identical study in five subjects 8 months to 4 years after the original observation.

RESULTS

Substantial EAR's and DAR's well exceeding significant percentage change values were recorded in 10 subjects (Table 1). This group will

Table 1

Type of the post-placebo asthmatic responses. Maximum intensity and mean percentage change in lung function during two defined periods following antigen challenge

Patient	Sig % change	Biphasic responders	
		0–1.5 h	3.5–7.5 h
1	10	–76 (–44 ± 25)	–28 (–13 ± 11)
2	11	–67 (–60 ± 5)	–60 (–42 ± 13)
3	3	–43 (–24 ± 11)	–12 (–8 ± 2)
4	10	–15 (–9 ± 4)	–35 (–32 ± 2)
5	3	–87 (–40 ± 32)	–19 (–10 ± 4)
6	5	–42 (–30 ± 10)	–44 (–26 ± 14)
7	11	–70 (–49 ± 16)	–45 (–31 ± 8)
8	9	–71 (–58 ± 12)	–68 (–48 ± 18)
9	6	–67 (–54 ± 14)	–14 (–10 ± 4)
10		–20 (–10 ± 8)	–40 (–20 ± 15)
Predominant EAR			
11	6	–57 (–43 ± 13)	0
12	9	–63 (–48 ± 10)	0
Predominant DAR			
13	4	0	–70 (–5 ± 24)

The range in lung function for the specific time period is shown in brackets. This was calculated by averaging the six lung function values in time period 0–1.5 h and five lung function values in the period 3.5–7.5 h. The sig % change value represents individual diurnal variation.

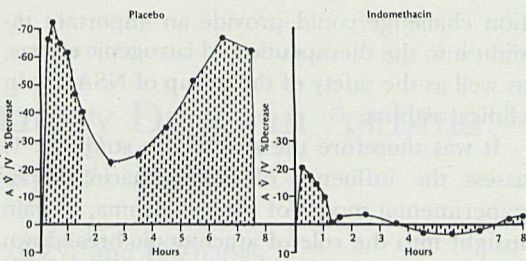


Fig. 1. Inhibition of the asthmatic response by pretreatment with indomethacin (subject 8, Table 2).

be referred to as the biphasic responders. Substantial EAR's with no DAR were recorded in two individuals – this subgroup was coined the predominant early asthmatic responders. In one patient, a predominant delayed asthmatic responder, no EAR, but a clear DAR was recorded.

Indomethacin pretreatment

On indomethacin pretreatment the baseline A V/V value prior to antigen challenge was within the Sig % change for each individual and similar to the placebo pretreatment value. Changes in A V/V at time points following antigen challenge were expressed as a percentage of the pre-challenge value (Fig. 1). These values were plotted against their respective time points. The area under this curve was used as a measure of total antigen response in time before and after indomethacin pretreatment. The difference in area between placebo and indomethacin pretreatment expressed as a percentage of the area under the placebo treatment curve was used to determine the percentage inhibition or enhancement of antigen response following indomethacin pretreatment. This was calculated for the time periods 0–1.5 h (EAR) and 3.5–7.5 h (DAR). The following formula was employed.

$$\frac{\text{Area under placebo curve} - \text{area under indomethacin curve}}{\text{area under placebo curve}} \times 100$$

= percentage inhibition or enhancement.

The percentage inhibition or enhancement caused by indomethacin pretreatment is shown in Table 2. In six of the 12 patients in whom EAR's were recorded, the reaction during this phase was suppressed by indomethacin pretreatment. No change was recorded in four individuals, and in two an enhancement of the first phase was found. DAR's were recorded in 11 of the 13 subjects. In 10 of these reactions the late phase was inhibited by indomethacin and in one subject the late phase response remained unchanged. A 68% and 66% inhibition of the DAR was recorded respectively in the two sub-

jects whose EAR's were enhanced by indomethacin pretreatment (Table 2: 5 and 6). The degree of inhibition of the DAR recorded in the subjects was substantial: 100% in four individuals and more than 40% in another six. Of the subjects in whom the indomethacin study was repeated, similar inhibition of the DAR reaction was recorded where previously it had been suppressed in all five individuals.

DISCUSSION

The role of indomethacin in asthma therapy remains a controversial issue. It incurs the potential to cause severe iatrogenic airways obstruction, but may on theoretical grounds have a positive therapeutic role in asthma. The inability of several research groups to demonstrate a substantial inhibitory effect on antigen-induced asthma, cast doubt on the meaningful participation of bronchoconstrictor prostaglandin breakdown products in the mechanism of allergic airways obstruction (12, 24). These clinical findings are in conflict with *in vitro* results in which evidence of participation of the cyclooxygenase pathway in immediate hypersensitivity reactions of lung fragments has been demonstrated. Evidence was found that these spasmogenic prostaglandin breakdown products participate in the causation of bronchial smooth muscle contraction and inhibition of this effect by indomethacin (5, 21). This discrepancy between the clinical and *in vitro* studies probably relates to the study design, in as much as the inhibitory influence of indomethacin during inhalation challenge was related to the EAR only (12, 24). The influence of indomethacin on the EAR in this study suggests that in individual asthmatics spasmogenic products of the arachidonic cascade, although not major determinants, may participate in the early response. The contention is supported by the inhibition of the EAR in six individuals and enhancement of the reaction in another two subjects. The unchanged EAR's in four patients suggests different spasmogenic mechanisms in this subgroup. The pattern of the responsiveness to indomethacin pretreatment was not en-

Table 2

The effect of indomethacin pretreatment on antigen response

Patient	% Inhibition (+) or enhancement (-) 0-1.5 h	% Inhibition (+) or enhancement (-) 3.5-7.5 h
<i>Biphasic responders</i>		
1	+94	+10
2	+30	-16*
3	+13*	+100
4	0*	+89
5	-45	+68
6	-46	+66
7	+48	+77
8	+81	+100
9	+44	+100
10	+ 2*	+100
<i>Predominant EAR</i>		
11	+86	-
12	- 3*	-
<i>Predominant DAR</i>		
13	-	+43

The values represent the percentage inhibition (+) or enhancement (-) of antigen response due to indomethacin pretreatment. This was calculated from the difference in areas under the percentage time curves, with placebo and indomethacin pretreatment, expressed as a percentage of the area under the placebo pretreatment curve.

$$\frac{\text{Area under placebo curve} - \text{Area under indomethacin curve}}{\text{Area under placebo curve}} \times 100$$

= percentage inhibition or enhancement.

All percentages are significant except where indicated by * (Wilcoxon signed-rank test for paired data).

tirely reproducible, however, as in one of five subjects an EAR reaction, which was suppressed initially, appeared to be enhanced when the study was repeated 8 months later.

The mechanisms underlying the DAR may differ completely from those of the EAR; the later phase of the asthmatic response appears to be more representative of clinically severe asthma (28). Experimental induction of the DAR has been held responsible for prolonged postchallenge hyperreactivity and spontaneous asthma (1, 4, 20). The controversy on the influence of NSAID's on antigen-induced asthma, was re-opened by Fairfax and co-workers when they demonstrated in four patients, partial inhibition of the DAR with a single dose of three NSAID's prior to antigen challenge (11). In the present study pretreatment for 72 h was employed and effective suppression of the delayed response was achieved as demonstrated by the 65% to a 100% inhibition in eight of the 11 delayed asthmatic responders. This influence of indomethacin on the postchallenge asthmatic response also appears to be consistent, because it was repeatedly demonstrated in five subjects.

Due to the uncertainty of the exact underlying mechanism in the DAR, the specific therapeutic effect of indomethacin in suppressing the DAR as shown, must remain speculative. The concept of an IgE-mediated delayed inflammatory skin reaction in which thromboxane figures as a prominent mediator with suppression of vascular permeability by indomethacin may represent an analogue pathogenesis to events which cause delayed airways obstruction (7, 8, 9, 25). The fact that it has pharmacological effects on the DAR similar to those of corticosteroids also suggests that indomethacin may act by means of inhibition of an allergic inflammatory mechanism.

Clinicians use NSAID's with caution in allergic asthmatics as these agents have been implicated in the airways obstruction which may ensue. This obstruction may be of prolonged duration, as has been documented in 8–19% of adult and 13% of childhood asthmatics (19, 26, 27). The baseline A V/V was remarkably consistent during indomethacin pretreatment, and induction of a severe degree of airways ob-

struction was not in evidence. Continuous treatment with NSAID appears safe, since desensitization by continuous intake of salicylates has been described in sensitive asthmatics (22). The risk of induction of sensitivity to NSAID by infrequent long-term therapy needs to be considered. None of the patients who participated in the repeat study had any problems while on the second course of active therapy. Enhanced first phase responses were recorded in two patients while on indomethacin treatment and also in one subject who was restudied. Did indomethacin enhance antigen sensitivity in these patients? The possibility cannot be ruled out entirely, but seems unlikely for two reasons. In all three subjects the first phase response terminated spontaneously and the delayed reaction was suppressed in spite of the enhanced first phase response. The delayed phase correlates well with enhanced bronchial sensitivity and should have occurred in concert with the EAR if greater antigen sensitivity had been induced (3, 28). Enhanced first phase reactivity due to recurrent antigen inhalation could explain this observation. As a general rule, patients with a history of iatrogenic airways obstruction due to NSAID should not be exposed. Observations for 2–4 h after the initial administration in high-risk patients should be an essential precaution. This study establishes the safety of indomethacin treatment during the active phase of asthma. Consistent inhibition of the DAR, conceivably by suppression of products of the arachidonic cascade, suggests that this agent may have a place as a prophylactic form of therapy in asthma. In this context its role as a partial or complete substitute for steroids in dependent asthmatics needs further study.

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