

# Inhibition of idiosyncratic reactions to aspirin in asthmatic patients by clemastine

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**ABSTRACT** An H<sub>1</sub>-receptor blocking antihistamine, clemastine, taken before aspirin gave complete or partial protection against flushing, rhinorrhea, cough, and headache in ten asthmatic patients with idiosyncrasy to aspirin. In five of the ten patients aspirin-precipitated bronchoconstriction was also reduced or prevented after pretreatment with clemastine. Thus histamine appears to play a part in the production of most non-respiratory symptoms occurring after aspirin ingestion in intolerant patients with asthma. Bronchial reactions might depend partly on histamine and partly on the action of other spasmogens. It is suggested that inhibition of prostaglandins of the E series by aspirin-like drugs plays a crucial part in the release of histamine from tissue stores in aspirin-sensitive asthmatic patients. Clemastine might be of use in the treatment of acute reactions to aspirin.

In some patients with bronchial asthma ingestion of aspirin leads to bronchoconstriction often accompanied by rhinorrhoea, redness of the face, and conjunctival injection (Samter and Beers, 1968). Similar reactions can be evoked by other analgesics which inhibit the activity of cyclo-oxygenase (Szczeklik *et al*, 1975), the enzyme that converts arachidonic acid into prostaglandin endoperoxides. It has been suggested that hypersensitivity reactions to analgesics in patients with bronchial asthma are not of immunological origin, but are due to inhibition of prostaglandin biosynthesis in their respiratory tracts (Szczeklik *et al*, 1975) and more specifically, to blockade of the generation of prostaglandins of the E series (PGEs), which accounts for the idiosyncrasy to analgesics. The evidence in favour of this hypothesis has been summarised by Szczeklik and Gryglewski (1978).

PGEs might exert their special defensive role in patients with aspirin-induced asthma through at least two mechanisms. Firstly, they are potent bronchodilators (Cuthbert, 1969) and, secondly, they inhibit histamine release from its stores (Kaliner and Austen, 1975). Removal of PGEs by analgesics would, therefore, deprive aspirin-sensitive patients of a bronchodilator, and would promote the release of histamine, to which these

patients respond dramatically (Samter and Beers, 1968; Szczeklik *et al*, 1977).

## Methods

Ten patients (eight women, two men) aged 22 to 57 years, with a diagnosis of aspirin-induced asthma were studied. They were all in clinical remission. Three were on maintenance therapy with prednisolone, 10 mg daily. Sodium cromoglycate was stopped 15 days before the study, and bronchodilator drugs were withdrawn eight hours beforehand.

The challenge tests were done in the morning after a light breakfast. After obtaining written consent, aspirin (20-60 mg) or placebo (100 mg lactose) were given by mouth. Clinical symptoms and peak expiratory flow (PEF) were recorded before giving the drug and every 30 minutes over four to five hours. A few days later, clemastine in a daily dose of 3 mg was taken by mouth for two consecutive days. On the third day 2 mg of clemastine was taken by mouth followed by a challenge test with aspirin two hours later. The dose of aspirin and the method used during this second challenge were the same as during the first one.

Uncomfortable symptoms were relieved by  $\beta_2$

stimulants or aminophylline. PEF was measured by a Wright peak-flow meter.

**Results**

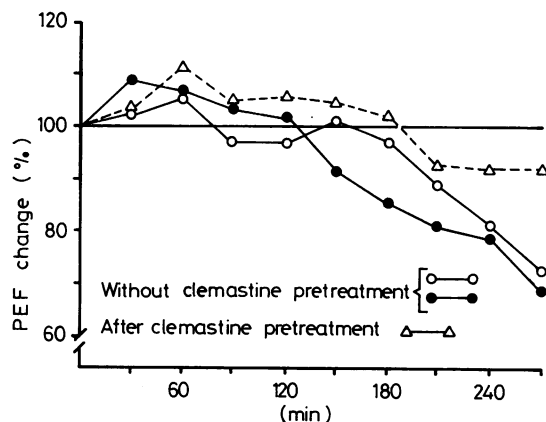
Results of challenge tests with aspirin were positive in all patients. Dyspnoea appeared and a fall in PEF by 21–50% of initial values was recorded (see table). Accompanying symptoms included watery rhinorrhea in six patients, vivid scarlet flushing of head and neck in six patients, and cough in two. All these changes began to appear not sooner than 60 minutes after aspirin ingestion and increased with time.

Before the second challenge test, which followed clemastine administration, the initial PEF values did not differ significantly from those obtained at the first challenge ( $p > 0.1$ ). In three patients (2, 5, and 7) clemastine pretreatment resulted in total prevention of both dyspnoea and PEF fall. In two others (3 and 4) the severity of dyspnoea induced by aspirin decreased as judged by subjective symptoms, auscultation, and PEF measurements. In the other two patients (6 and 9) there was a delay of 30–50 minutes in the onset of dyspnoea, which then developed precipitously and was of similar magnitude as during the control challenge. In the remaining three patients (1, 8, and 10) the time of onset of the obstruction, its severity, and PEF changes were similar during those two challenges.

Clemastine also exerted total protection against flushing in three of six patients, and considerably attenuated the severity of the flush while delaying its onset by 60–120 minutes in the remaining three subjects. Of six patients who responded with rhinorrhea to aspirin, clemastine pretreatment resulted in lack of nasal discharge at the repeated challenge in three (cases 5, 7, and 9) and attenuation and delay of this reaction in the remaining three (2, 6, and 8). Clemastine also gave full protection against cough in two patients and against headache and tinnitus in another one.

Nine days after the second challenge, a third one using the same dose of aspirin was repeated in two patients. Clinical symptoms and PEF behaviour were very much the same as during the first challenge, preceding clemastine administration (figure).

Figure: A line graph showing PEF change (%) over time (min) for three patients. The y-axis ranges from 60 to 120. The x-axis ranges from 0 to 240. Three data series are shown: 'Without clemastine pretreatment' (open circles), 'After clemastine pretreatment' (open triangles), and 'After clemastine pretreatment' (filled circles). The 'Without clemastine pretreatment' series shows a sharp decline in PEF after 60 minutes. The 'After clemastine pretreatment' series (both open and filled triangles) show a much smaller decline, remaining above 80% PEF change throughout the 240-minute period.



*Bronchial response to 30 mg aspirin challenges in a 37-year-old man. Aspirin alone was administered first (-○-○-), five days later after clemastine pretreatment (-△-△-), and again 14 days from first challenge (-●-●-).*

Lactose produced neither clinical symptoms nor changes in PEF greater than 15% of initial values in any of the patients studied.

**Discussion**

The results obtained indicate that some adverse symptoms produced by aspirin in asthmatic patients with idiosyncrasy to this drug are caused

*Percentage change from baseline of peak flow rate before and after clemastine pretreatment*

Patient No	Aspirin dose mg	Minutes after aspirin											
		120		150		180		210		240		270	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	20	-18	-17	-25	-25	-38	-29	-43	-29	-40	-43		
2	30	+ 2	+ 6	- 8	+ 5	-14	+ 2	-19	- 7	-21	- 8	-31	- 8
3	30	-17	-11	-27	-11	NM	-18	NM	-25				
4	40	- 1	+ 5	- 1	0	- 2	+ 2	-15	+ 2	-25	+ 5	-37	-12
5	40	-14	- 1	-14	0	-37	- 4	NM	0	NM	- 3	NM	+ 3
6	40	- 6	+ 6	-25	+11	-27	- 2	-31	-38				
7	40	-14	- 8	-27	- 8	-41	-11						
8	50	- 2	- 1	- 2	- 1	- 7	- 3	- 6	- 4	- 5	- 1	-21	-22
9	60	- 6	+11	-29	+ 1	-22	-10	-34	-13	NM	-27		
10	60	-11	-11	-21	-23	-25	-50	-52	-52				

NM=Not measured.

by endogenous release of histamine. Thus clemastine, an  $H_1$ -receptor blocking antihistamine, gave good protection against aspirin-induced flushing, a symptom observed commonly also after administration of histamine to man. Inhibition of rhinorrhoea, cough, and headache point also to the participation of histamine in the development of these symptoms.

The protective effect of clemastine on aspirin-induced bronchoconstriction was less evident. The protection was complete in some patients, partial in some, and absent in others. It might, therefore, be assumed that histamine is not the sole final mediator responsible for aspirin-induced bronchoconstriction in hypersensitive subjects. Other spasmogens might play a more important part in those patients who experienced little or no protection from clemastine.

Participation of histamine in aspirin-induced bronchoconstriction was suggested by recent studies. Thus Stevenson *et al* (1976) observed significant rises in plasma histamine after aspirin challenge in aspirin-sensitive asthmatics, but not in asthmatic patients without this sensitivity or in control subjects. Several authors have also reported on inhibition of aspirin-precipitated bronchospasm by sodium cromoglycate in hypersensitive patients (Basomba *et al*, 1976; Delaney, 1976; Martelli and Usandivaras, 1977; Pasargiklian *et al*, 1977). Sodium cromoglycate appears to stabilise mast cell membranes and to inhibit the action of intravenous histamine that is dependent on  $\alpha$ -adrenergic receptors (Kerr *et al*, 1970). This action of sodium cromoglycate might explain its good therapeutic effects in some patients with aspirin-induced asthma (Gwin *et al*, 1977; Szczeklik *et al*, 1977).

We believe (Szczeklik *et al*, 1975, 1977) that the release of histamine from its stores here discussed results from blockade generation of PGEs by analgesics. This concept is supported by the results of studies showing that in-vitro PGEs inhibit release of histamine from human lung slices (Walker, 1973) and human basophil preparations (Lichtenstein and Bourne, 1971). Furthermore, the antigen-induced release of histamine from human basophils is considerably increased after blockade of PGEs generation by aspirin (Okazaki *et al*, 1977). The stabilising effect of PGEs on mast cells and basophils appears to be connected with their ability to increase cyclic AMP (Kaliner and Austen, 1975). It should therefore be noticed that prostacyclin, a recently discovered arachidonate metabolic (Gryglewski *et al*, 1976), is a more potent stimulator of cAMP than PGEs (Gorman *et al*, 1977). Prostacyclin, however,

appears to act primarily in the vascular bed, as a circulating hormone (Gryglewski *et al*, 1978). Furthermore, it has little, if any, bronchodilator effect in asthmatic patients, including those with aspirin-sensitive asthma (Szczeklik *et al*, 1978).

Our results suggest that clemastine might be helpful in the treatment of acute adverse reactions to aspirin. An inhalation should be most suitable in these cases, since inhaled clemastine causes bronchodilatation in patients with asthma (Nogrady *et al*, 1978). It remains to be seen whether prolonged treatment with clemastine could benefit patients with aspirin-induced asthma.

## References

- Basomba, A, Romar, A, Peláez, A, Villalmanzo, I G, and Campos, A (1976). The effect of sodium cromoglycate in preventing aspirin-induced bronchospasm. *Clinical Allergy*, **6**, 269–275.
- Cuthbert, M F (1969). Effect on airways resistance of prostaglandin  $E_1$  given by aerosol to healthy and asthmatic volunteers. *British Medical Journal*, **4**, 723–726.
- Delaney, J C (1976). The effect of sodium cromoglycate on analgesic-induced asthmatic reactions. *Clinical Allergy*, **6**, 365–368.
- Gorman, R R, Bunting, S, and Miller, O V (1977). Modulation of human platelet adenylate cyclase by prostacyclin (PGX). *Prostaglandins*, **13**, 377–388.
- Gryglewski, R J, Bunting, S, Moncada, S, Flower, R J, and Vane, J R (1976). Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins*, **12**, 685–713.
- Gryglewski, R J, Korbut, R, and Ocetkiewicz, A (1978). Generation of prostacyclin by lungs in vivo and its release into arterial circulation. *Nature*, **273**, 765–767.
- Gwin, E, Kerby, G R, and Ruth, W E (1977). Cromolyn sodium in the treatment of asthma associated with aspirin hypersensitivity and nasal polyps. *Chest*, **72**, 148–154.
- Kaliner, M, and Austen, K F (1975). Immunologic release of chemical mediators from human tissues. *Annual Review of Pharmacology*, **15**, 177–189.
- Kerr, J W, Govindaraj, M, and Patel, K P (1970). Effect of alpha-receptor blocking drugs and disodium cromoglycate on histamine hypersensitivity in bronchial asthma. *British Medical Journal*, **2**, 139.
- Lichtenstein, L M, and Bourne, H R (1971). Inhibition of allergic histamine release by histamine and other agents which stimulate adenylyl cyclase. In *Biochemistry of Acute Allergic Reactions*. Edited by K F Austen and E L Becker, p 161. Blackwell, Oxford.
- Martelli, N A, and Usandivaras, G (1977). Inhibition of aspirin-induced bronchoconstriction by sodium cromoglycate inhalation. *Thorax*, **32**, 684–690.

- Nogrady, S G, Hartley, J P R, Handslip, P D J, and Hurst, N P (1978). Bronchodilatation after inhalation of the antihistamine clemastine. *Thorax*, **33**, 479-482.
- Okazaki, T, Ilea, V S, Rosario, N A, Reisman, R E, Arbesman, C E, Lee, J B, and Middleton, E (1977). Regulatory role of prostaglandin E in allergic histamine release with observations on the responsiveness of basophil leukocytes and the effect of acetylsalicylic acid. *Journal of Allergy and Clinical Immunology*, **60**, 360-366.
- Pasargiklian, M, Bianco, S, Allegra, L, Moavero, N E, Petrigni, G, Robuschi, M, and Grugni, A (1977). Aspects of bronchial reactivity to prostaglandins and aspirin in asthmatic patients. *Respiration*, **34**, 79-91.
- Samter, M, and Beers, R F (1968). Intolerance to aspirin. *Annals of Internal Medicine*, **68**, 975-983.
- Stevenson, D D, Arroyave, C M, Bhat, K N, and Tan, E M (1976). Oral aspirin challenges in asthmatic patients: A study of plasma histamine. *Clinical Allergy*, **6**, 493-506.
- Szczeklik, A, and Gryglewski, R J (1978). Prostaglandins and aspirin-sensitive asthma. *American Review of Respiratory Disease*, **118**, 779-780.
- Szczeklik, A, Gryglewski, R J, Czerniawska-Mysik, G (1975). Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *British Medical Journal*, **1**, 67-69.
- Szczeklik, A, Gryglewski, R J, and Czerniawska-Mysik, G (1977). Clinical patterns of hypersensitivity to non-steroidal anti-inflammatory drugs and their pathogenesis. *Journal of Allergy and Clinical Immunology*, **60**, 276-284.
- Szczeklik, A, Gryglewski, R J, Nizankowska, E, Nizankowski, R, and Musiał, J (1978). Pulmonary and anti-platelet effects of intravenous and inhaled prostacyclin in man. *Prostaglandins*, **16**, 651-660.
- Walker, J L (1973). The regulatory function of prostaglandins in the release of histamine and SRS-A from passively sensitized human lung tissue. In *International Conference on Prostaglandins*, edited by A Bergstrom and S Bernhard, (Advances in biosciences), vol 9, p 235. Pergamon, Oxford.

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