

The effect of sodium cromoglycate in preventing aspirin induced bronchospasm

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Summary

Seventeen patients with aspirin-induced asthma were studied, the majority being intolerant to more than one analgesic. In addition to asthma, eleven patients had sinusitis and eight had nasal polyps. Serum IgE levels were normal with a mean of 295 iu/ml. However, some patients had positive cutaneous and PK tests against inhalants and non-analgesic drugs.

Spirometry showed the bronchial obstruction to be mild. However, all patients were hyper-reactive to acetylcholine. Oral provocation tests with aspirin alone and also with the prior administration of sodium cromoglycate (SCG) by inhalation were performed and the results assessed by spirometry and clinical examination.

The results suggest that the obstruction is probably due to oedema of the bronchial mucosa together with pulmonary congestion rather than a simple spasm of the bronchi.

SCG was found to prevent significantly the ventilatory obstruction induced by aspirin.

It is suggested that non-immunological factors are responsible for the asthma and that SCG may have an effect on the altered receptors protecting them from the action of aspirin on kinins.

Introduction

The possibility that the oral administration of aspirin may precipitate an asthmatic attack was first described in 1919 (Cooke, 1919). Despite extensive studies by several investigators (Van Leeuwen, 1924; Bruce Pearson, 1963; Samter & Beers, 1967) the pathogenesis of the syndrome in which patients have bronchial asthma, sinusitis with or without nasal polyps and who are sensitive to aspirin and other analgesics (ASA-Triad) remains uncertain.

These patients are difficult to manage therapeutically, this difficulty being increased by the uncontrolled administration of analgesics which often result in severe ventilatory obstruction (Blamoutier, 1954; Francis, 1929; Rose & Radermecker, 1971).

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Several hypotheses as to the cause of this syndrome have been suggested. One theory is that the symptomatology is brought about by a direct activation of complement due to a deficiency of an enzymatic inhibitor (Yurchak, Wicher & Arbesman, 1970). It has also been suggested that there is an alteration of the pulmonary nociceptive receptors so that aspirin, a kinin antagonist, acts as an agonist thus reproducing the pharmacological actions of kinins (Samter & Beers, 1967). An immunological hypothesis has not been confirmed, although it has been suggested that the presence of acetyl salicylic anhydride in commercial samples of aspirin could induce, after an aspirilation process, the formation of anti-aspiryl antibodies and these could be responsible for symptoms (De Weck, 1971).

It is probably wise to distinguish between a true allergy to aspirin and the syndrome under discussion since the pathogenesis of the two may be entirely different.

The objective of this study was to investigate a group of patients with aspirin-induced asthma (ASA-Triad) in the hope of resolving some of the problems and also to assess the effect of sodium cromoglycate.

Materials and methods

Seventeen patients (six males and eleven females) were studied; they all had a history of asthma and an intolerance to analgesics. The asthma was confirmed by physical examination and spirometry. Aspirin sensitivity was strongly suggested by the history and was confirmed by challenge tests.

The mean age was 43 years (range 28–60) and the mean age of onset of asthma was 34 years (range 10–57). Eleven patients had an associated sinusitis and eight had nasal polyps or had had a polypectomy. A blood eosinophilia of more than 400 cells/mm³ was found in ten patients. Six patients had a positive skin test to inhalants (house dust—4, pollens—2); four had an immediate skin reaction test to non-analgesic drugs (penicillin—2, streptomycin—1, chloramphenicol—1) (see Table 1).

Intolerance to analgesics was clinically present in all patients. Three were sensitive to only one analgesic whilst the remainder were sensitive to two or more (Table 2). In general, sensitivity was clear from the past history but in those in which no evidence of previous use was obtained the patient was challenged with an oral administration of an analgesic and a positive result obtained.

Five patients had skin symptoms (cold urticaria—2, dermatitis solaris—1, urticaria factitia—1, nickel dermatitis—1); one patient was sensitive to egg.

The patients had been under medical supervision for up to 5 years, and in general their asthma had been poorly controlled with bronchodilators. Corticosteroid therapy was frequently required and, with few exceptions, the use of Intal (SCG) had proved to be ineffective.

Pulmonary function and bronchial provocation tests with acetylcholine were performed in all patients. Oral provocation with aspirin alone and with pre-treatment by SCG was carried out in all the patients.

Assessment of pulmonary function was made before and after the oral administration of aspirin; the initial dose was 20–50 mg depending on the sensitivity of the patient. A fall of 20% or more in the FEV₁ was considered significant; if the FEV₁ was less than 20% a second challenge was carried out after 60–90 min with the same or larger dose of aspirin.

One month later the same patients were rechallenged using the same dose of aspirin which had previously produced a 20% fall in the FEV₁; however, in this

Table 1. Clinical details of seventeen patients with aspirin-induced asthma

Details	No. of patients
Age of onset of asthma	34 (range 10–57)
Chronic asthma + aspirin-induced asthma	16
Aspirin-induced asthma without chronic asthma	1
Sinusitis	11
Nasal polyps or polypectomy	8
Eosinophilia	10
Positive skin tests to inhalants	6
House dust	4
Pollens	2
Positive skin tests to non-analgesic drug	4
Penicillin	2
Streptomycin	1
Chloramphenicol	1

instance SCG was administered 20 min before the aspirin at a dose of 2×20 mg spin-caps; a further four capsules were administered for 2–3 hr following provocation.

All the provocation tests were performed under similar conditions in that medication was withheld for 3 days and the patients were relatively asymptomatic.

Serum IgE was measured in all patients by radioimmunoassay, using the Phadebas IgE kit (Pharmacia). For controls, serum was examined from ninety-three healthy volunteers and 190 patients diagnosed as extrinsic asthmatics.

Blood gases were analysed in five patients before and after provocation with aspirin. A Minjhardt spiograph with incorporated He UG45 analyser was used for measuring the residual volume.

Results

The mean baseline spirometry is shown in Table 3. In general, the results were variable as one would expect from the lability of the asthma symptoms. Baselines obtained before each challenge produced similar results.

Following acetylcholine there was an immediate reaction with a fall of 42% in FEV₁ and 23% in VC, expressed as a percentage of the baseline value. Sixteen patients showed bronchial hyper-reactivity to low doses of acetylcholine (100–500 gammas); one reacted to higher doses (5000 gammas). Recovery occurred within 15 min following the inhalation of orciprenaline.

Table 2. Response to analgesics in seventeen patients

No. of patients	3	7	2	3	1	1	Total
Aspirin	+	+	+	+	+	+	17
Aminopyrine	—	+	+	+	—	—	12
Mephenamic acid	—	—	+	+	+	+	7
Glaphenine	—	—	—	+	—	+	4
Dipirone	—	—	—	+	+	—	4

+, Sensitivity; —, no sensitivity.

Table 3. Mean of the spirometric basal values found in seventeen patients with aspirin induced asthma expressed as a percentage of the respective theoretical values obtained from CECA tables

	VC	FEV ₁	RV	TLC	RV/TLC	FEV ₁ /VC	MBC	Mixing time
$\bar{x}$	79	65	176	105	42	62	72	2' 32"
s	19	21	38	14	10	11	24	27"

VC, Vital capacity; FEV₁, forced expiratory volume in 1 sec; RV, residual volume; TLC, total lung capacity; MBC, maximal breathing capacity.

$\bar{x}$, Arithmetic mean; s, standard deviation of sample.

The challenge with acetylsalicylic acid (mean dose 75 mg, s.d. 50 mg) produced a fall of 45% (s.d. 13%) in FEV₁ and 30% (s.d. 13%) in VC, with an increase of 33% (s.d. 33%) in residual volume, but no change in total lung capacity. The maximum change appeared within 1 hr of the administration of the drug and was accompanied by clinical symptoms of dyspnoea, cough, bronchial hypersecretion, oculo-nasal

Table 4. FEV₁ readings before challenge, after aspirin and after SCG plus aspirin

Patient no.	Aspirin			SCG plus aspirin			SCG effect
	Baseline	After challenge	Variation	Baseline	After challenge	Variation	
1	2.450	1.400	-43%	2.250	1.300	-42%	+1‡
2	3.900	3.100	-26%	3.600	2.520	-30%	-4‡
3	1.200	920	-23%	980	1.000	+2%	+25*
4	1.550	910	-41%	1.350	1.600	+19%	+60*
5	2.500	1.175	-53%	2.550	1.780	-30%	+23‡
6	3.450	2.350	-32%	3.300	3.700	+12%	+44*
7	3.350	2.080	-38%	3.420	3.490	+2%	+40*
8	1.650	900	-45%	1.700	710	-58%	-13‡
9	2.350	590	-75%	2.450	2.350	-4%	+71*
10	1.350	700	-48%	1.350	530	-61%	-13‡
11	1.280	600	-47%	1.000	1.250	+25%	+72*
12	2.100	1.320	-37%	2.200	1.320	-40%	-3‡
13	1.100	640	-42%	950	1.060	+12%	+54*
14	1.950	970	-50%	1.900	1.290	-32%	+18‡
15	900	380	-58%	700	480	-43%	+15‡
16	1.600	535	-66%	2.050	1.350	-34%	+32‡
17	1.050	740	-33%	1.100	990	-10%	+23*
Mean	1.984	1.136	-45%	1.931	1.572	-18%	+26
s.d.	905	734	13	917	938	27	28
P		< 0.005			N.S.		< 0.001

Variation = (value after challenge/baseline - 1) × 100.

SCG effect is the difference between the variation after SCG plus aspirin and aspirin alone.

* Total protection: SCG effect ≥ |Variation after Aspirin| - 10; † Partial protection: |Variation after Aspirin| - 10 > SCG effect > 10; ‡ No protection: SCG effect ≤ 10.

congestion, lachrymation, oedema of the nasal mucosa and malaise. Three patients developed lipothymia without shock, with urticaria, facial oedema and a vagal digestive reaction resulting in vomiting and diarrhoea. It was noted that inhaled orciprenaline was ineffective in alleviating the bronchospasm and injection of adrenaline and giving of corticosteroids was necessary in order to bring the patients back to baseline values within about 30 min; even so, two patients developed a late reaction after 5–6 hr.

In five patients in whom blood gasses were estimated there was a significant decrease of 18 mm Hg in the P_{O_2} and an increase of 3.5 mm Hg in P_{CO_2} .

When the challenge with aspirin was preceded by SCG there was a significant degree of protection as shown by a mean fall in FEV_1 of 18% (s.d. 27%, $P < 0.001$) and VC of 12% (s.d. 21%, $P < 0.001$). The changes in FEV_1 with aspirin alone and with the prior administration of SCG for all seventeen patients are shown in Table 4. Total protection was achieved with SCG in eight, partial protection in four and no protection in five. There was no changes in non-respiratory symptoms, even in those who had full bronchial protection. After 15 min, two patients (nos. 4 and 11) who initially showed evidence of bronchial obstruction, showed an improvement in FEV_1 and VC from their baseline values and auscultation of the chest became quite normal.

The serum IgE levels were within the range of normality, the mean for seventeen patients was 295 iu/ml (range 45–750); in 190 allergic asthmatics the mean was 1235 iu/ml and this difference was significant ($P < 0.0005$). The mean IgE values in ninety-three healthy subjects was 291 iu/ml.

Discussion

In this study the ratio of females to males was 2:1 and the predominance of females has been noted by other investigators. The association of asthma, sinusitis with or without nasal polyposis and aspirin intolerance has given rise to the syndrome ASA-triad. However, in our experience these three symptoms do not always co-exist and therefore we consider that this terminology should be dropped.

Some of our patients were sensitive to a range of drugs chemically unrelated to analgesics and this, together with a blood eosinophilia and reaginic type symptoms, could suggest that the disease was immunologically dependent on IgE; however, serum levels of this immunoglobulin do not support this hypothesis; no patient had serum IgE above the upper limit of normal, thus we are in agreement with other investigators (Vatanasuk, Hornbrook & Kohler, 1971).

There are several reports regarding intolerance to various analgesics or their derivatives; aminopyrine, indomethacin and tartrazine (Samter & Beers, 1967); paracetamol, mephenamic acid, dextropropoxyphene (Smith, 1971), 2-hydroxybenzyl alcohol, 4-hydroxybenzoic acid (Juhlin, Michaelsson & Zetterstrom, 1972). We are not aware of any published reports of intolerance to glaphenine which is a newer analgesic chemically derived from quinoline and anthranilic acid.

To date we have found four cases intolerant to this substance which throws some doubt on its value as a safe analgesic as has been suggested (Mathov, 1969).

The oral administration of aspirin induced severe bronchial obstruction and symptomatic changes; generally recovery after challenge was slow and the administration of orciprenaline often ineffective so that it was necessary to administer adrenaline and steroids and to institute secondary measures. In a few cases a late reaction occurred 5–6 hr after challenge; the significance of this is not known.

Generally the bronchial obstruction produced an abrupt fall in the dynamic parameters and a somewhat smaller but significant fall in the static parameters. The changes in blood gases indicated some degree of hypoventilation induced by the ventilatory obstruction.

The spirometric results, together with the clinical symptoms following an aspirin challenge, suggest that the bronchial obstruction may be due predominantly to oedema of the mucosa with pulmonary congestion rather than spasm of the bronchial musculature. It has been suggested (Samter & Beers, 1967) that aspirin normally protects the nociceptive receptors against the action of kinins but that in aspirin sensitive subjects it stimulates these receptors. Thus it acts as an agonist and has a kinin-like activity.

Sodium cromoglycate has been shown in this experiment to protect against aspirin-induced bronchial obstruction. The protection was complete in some patients, partial in others and without effect in 31%. It is difficult to believe that the action of SCG could be solely one of protecting mast cells. It has been shown (Kerr, Govindaraj & Patel, 1970) that SCG inhibits the action of intravenous infusion of histamine which is dependent on alpha-adrenergic receptors and these authors suggest that SCG therefore stabilizes the cell membrane of these receptors thereby altering the calcium ion transport.

We suggest that SCG also acts on the bronchial nociceptors protecting them from the kinin-like activity of aspirin so that the normal action of aspirin prevails. The reason why the most sensitive patients were not protected by SCG could be a simple problem of dose. The fact that in two patients aspirin produced a reduction in the initial bronchospasm suggests that, when SCG fully protects the nociceptors the normal action of aspirin, which is to relax the bronchial musculature, comes into play.

Why so many patients were protected by SCG in this challenge study when they were not adequately controlled clinically by daily inhalations of Intal is not clear, unless it is simply a matter of dose. The therapeutic dose of Intal is 20 mg SCG four times daily; we gave 40 mg 20 min before the oral aspirin challenge and a further four doses of 20 mg SCG over the next 2–3 hr.

Oral challenges with aspirin are not without danger. Seven of the challenges led to a fall of more than 50% in FEV₁, one as much as 75%. In addition the reaction takes longer to develop than a standard inhalation antigen challenge with, for example, house dust mite, so that a fall of 50% or more in FEV₁ is far more distressing to the patient after an aspirin challenge. We would therefore not recommend oral challenges with aspirin to be adopted as a routine investigation, and, if they are done, they should be done with extreme care and constant supervision of the patient.

References

- BLAMOUTIER, P. (1954) Allergie vers l'aspirine dans malades d'asthme. *Semaine des Hôpitaux de Paris*, **30**, 1549.
- BRUCE PEARSON, R.S. (1963) Hypersensitivity to aspirin. In: *Salicylates* (Ed. by A.S. Dixon and K.B. Martin), p. 170. J. and A. Churchill, London.
- COOKE, R.A. (1919) Allergy in drug idiosyncrasy. *Journal of the American Medical Association*, **73**, 759.
- DE WECK, A.L. (1971) Immunological effects of aspirin anhydride, a contaminant of commercial acetylsalicylic acid preparations. *International Archives of Allergy and Applied Immunology*, **41**, 393.
- FRANCIS F. (1929) The prognosis of operation for removal of nasal polypi in cases of asthma. *The Practitioner*, **123**, 272.
- JUHLIN, L., MICHAELSSON, G. & ZETTERSTROM, O. (1972) Urticaria and asthma induced by food-and-

- drug additives in patients with aspirin hypersensitivity. *Journal of Allergy and Clinical Immunology*, **50**, 2, 92.
- KERR, J.W., GOVINDARAJ, M. & PATEL, K.P. (1970) Effect of alpha-receptor blocking drugs and disodium cromoglycate on histamine hypersensitivity in bronchial asthma. *British Medical Journal*, **ii**, 139.
- MATHOV, E. (1969) *Alergia a Drogas*, p. 316. Editorial Paidos, Buenos Aires.
- PATON, W.D.M. (1961) A theory of drug action based on the rate of drug-receptor combination. *Proceedings of the Royal Society of Biology*, **154**, 21.
- ROSE, B. & RADERMECKER, M. (1971) The pathogenesis of bronchial asthma. In: *Immunological Diseases* (Ed. by M. Samter), p. 860. Little, Brown and Company, Boston.
- SAMTER, M. & BEERS, R.F. (1967) Concerning the nature of intolerance to aspirin. *Journal of Allergy*, **40**, 5.
- SMITH, A.P. (1971) Response of aspirin-allergic patients to challenge by some analgesics in common use. *British Medical Journal*, **2**, 494.
- VAN LEEUWEN, W.S. (1924) A possible explanation for certain cases of hypersensitiveness to drugs in man. *Journal of Pharmacology and Experimental Therapeutics*, **24**, 25.
- VATANASUK, M., HORNBROOK, M.M. & KOHLER, R.F. (1971) Serum IgE and passive transfer in aspirin intolerance. *Annual Meeting of the American Academy of Allergy. Journal of Allergy*, **47**, 2.
- YURCHAK, M., WICHER, M. & ARBESMAN, C.E. (1970) Immunologic studies on aspirin. *Journal of Allergy*, **46**, 245.

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