

The effect of ketotifen on aspirin-induced asthmatic reactions

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Summary

The effectiveness of prophylactic treatment with ketotifen was assessed in ten asthmatic patients with aspirin idiosyncrasy in a randomized double blind trial. Increased airways obstruction following challenge with aspirin was significantly reduced when patients were pre-treated with ketotifen.

Introduction

Ketotifen, a cycloheptathiophene derivative, is a recently introduced, orally active drug having properties similar to those of sodium cromoglycate (SCG) (Von Wichert, 1980). Animal and clinical studies have shown it to be not only a relatively selective, potent and long acting histamine antagonist but also to possess marked anti-anaphylactic properties (Martin & Romer, 1978). Studies in atopic asthma have confirmed its good protective effects against allergen-induced bronchospasm (Szczeklik *et al.*, 1980).

Asthmatic patients with aspirin 'allergy' form a sub-group of intrinsic asthma. However, there is no satisfactory evidence that immunological factors are involved in the condition (Giraldo, Blumenthal & Spink, 1969). The structural dissimilarities between the analgesics which will induce asthmatic reactions in patients sensitive to aspirin would tend to confirm the view that this is an idiosyncratic reaction rather than an allergic response (Smith, 1971). However, the speed of onset of the symptoms of asthma and urticaria after analgesic ingestion in these patients bears a similarity to an immediate (type I) allergic response.

This study, using a double blind cross-over method, was undertaken to assess the effectiveness of ketotifen in the prevention of increased airways obstruction following analgesic challenge in ten asthmatic patients with established aspirin idiosyncrasy.

Patients and methods

Ten patients, six female and four male, with an age range of 36–67 years (mean 54.5 years) took part in the study. Each had the classical triad of nasal polyposis, asthma and aspirin sensitivity and their clinical features are outlined in Table 1. Previous oral

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Table 1. Clinical features of ten patients with aspirin idiosyncrasy

Patient	Age	Sex	Age of onset of			Number of polypectomies	Associated sensitivities
			Nasal polyps	Asthma	Aspirin sensitivity		
D.J.	58	F	38	25	25	6	—
L.T.	67	F	37	31	34	8	—
G.W.	62	F	44	48	48	2	Paracetamol
L.H.	44	M	10	27	30	3	—
P.K.	51	F	41	38	46	2	Ibuprofen Tetracycline
J.W.	68	M	52	60	60	4	Paracetamol
M.C.	36	F	28	23	23	1	Paracetamol
R.K.	45	M	32	39	41	2	—
B.K.	45	M	24	42	49	3	—
*M.B.	67	F	48	53	57	4	—

* All patients were non-atopic on skin-testing except patient 10—*D. pteronyssinus*; *A. fumigatus*

challenge with incremental doses of aspirin had confirmed this history of aspirin idiosyncrasy and determined the dose of aspirin to be used to challenge each patient in the present study. Patients taking SCG or antihistamines were asked to omit them from 24 hr prior to the start of the trial until its completion.

Initially, patients were challenged with an inert control capsule (a) to obtain baseline readings of the peak flow rate (PFR) and (b) to become familiar with the test conditions. Peak flow rate measurements, using a Wright peak flow meter, were made before swallowing the capsule and at 30 min intervals for 120 min afterwards; the best of three measurements being recorded each time.

Patients received ketotifen 1 mg twice daily or matched placebo over two consecutive three day periods in a double blind cross-over design. The treatments were given in a randomized order. Capsules were counted to assess that correct dosages had been given. At the end of each 3-day period, and 4 hr after the last dose, each patient was challenged orally with an amount of aspirin known to produce increased airways obstruction within 120 min.

Statistical analysis was by a sign test comparing patients' results during the two treatment periods.

Results

Ten patients took part in the trial. The mean percentage PFR changes recorded at 30-min intervals for 120 min after aspirin challenge (Table 2) shows that pre-treatment with ketotifen produces a statistically significant protection against increased airways obstruction at 90 and 120 min ($P < 0.05$). It can be seen that the effect of aspirin challenge after pre-treatment with ketotifen was similar to that following challenge with the lactose control (Fig. 1).

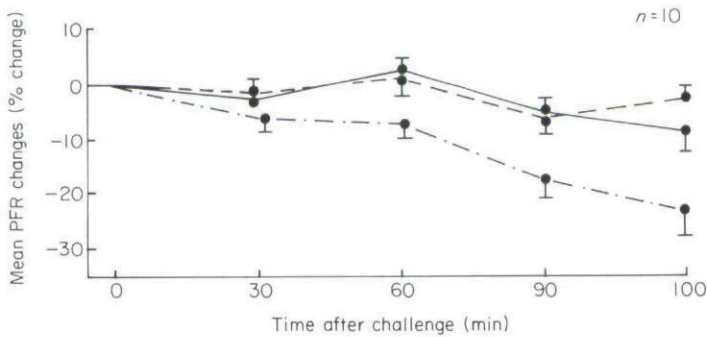
Discussion

This study of ten patients with asthma and aspirin idiosyncrasy demonstrates that

Table 2. Aspirin challenge following treatment with ketotifen and placebo ($n = 10$)

After challenge (min)	Mean % PFR changes		
	Lactose control	Aspirin	
		After Ketotifen	After Placebo
30	-1.0 (± 6.8)	-1.4 (± 10.11)	-6 (± 8.1)
60	+0.6 (± 6.4)	+2.7 (± 6.5)	-7.4 (± 11.4)
90	-4.8 (± 8.15)	-4.2 (± 10.2)	-16.6 (± 14.1)
120	-2.95 (± 7.8)	-6.4 (± 15.5)	-22.9 (± 19.8)

(Standard deviations are given in brackets)

**Fig. 1.** Aspirin challenge following treatment with ketotifen and placebo. ---, Lactose control; —, aspirin + ketotifen; - · -, aspirin + placebo.

ketotifen was effective in preventing increased airways obstruction in eight patients following challenge with aspirin. This confirmed the findings of an earlier study of two patients (Wuethrich, Radielovich & Debelic, 1978), and an open study with no placebo control (Szczeklik *et al.*, 1980), which showed similar protection in thirteen patients of fourteen challenged with aspirin.

The protective effect of ketotifen appears superior to that obtained in a previous study from this centre using inhaled SCG. In that study 20 mg SCG inhaled prior to challenge with aspirin protected against airways obstruction only three patients of nineteen challenged (Delaney, 1976). However, another study using larger inhaled doses (40 mg) in seventeen patients obtained complete protection in eight and partial protection in a further four (Basomba *et al.*, 1976). These patients also received a further 80 mg SCG over the 2–3 hr following challenge and protection in these cases may have been due to a bronchodilator effect of SCG (Chung & Jones, 1979).

However, it is possible that the larger dose of SCG is necessary to achieve the same effect as ketotifen in aspirin idiosyncrasy by stabilizing the mast cell membrane and inhibiting the release of spasmogens including histamine, 5-hydroxytryptamine and slow release substance of anaphylaxis (SRSA).

Significant rises in plasma histamine have been observed following aspirin

challenge in aspirin-sensitive asthmatics but not in other asthmatics or controls (Stevenson *et al.*, 1976). It has been shown that aspirin ingestion suppresses prostaglandin synthesis (Vane, 1971), and as prostaglandin E (PGE) inhibits the release of histamine from human lung slices and human basophil preparations (Walker, 1973), then the release of histamine from its stores following challenge may be due to blockade of PGE by aspirin. Support for this hypothesis is provided by the observation that antigen induced release of histamine from human basophils is considerably increased after blockade of PGE generation by aspirin (Okazaki *et al.*, 1977). The prophylactic protection afforded by ketotifen, demonstrated in this study, may therefore reflect its antihistaminic properties in much the same way as clemastine has been shown to prevent airways obstruction in patients sensitive to aspirin (Szczeklik & Serwonska, 1979).

In conclusion, this study demonstrates the effectiveness of ketotifen in preventing significant airways obstruction following aspirin challenge in asthmatics with aspirin idiosyncrasy. It is suggested that this protection is due either to ketotifen acting as a stabiliser of the mast cell membrane, preventing mediator release, or to its action as a histamine antagonist.

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