

Salicylate pre-treatment attenuates intensity of bronchial and nasal symptoms precipitated by aspirin in aspirin-intolerant patients

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Summary

Aspirin (ASA) and other non-steroidal anti-inflammatory drugs, which are cyclo-oxygenase (COX) inhibitors, precipitate asthmatic attacks in ASA-intolerant patients, while sodium salicylate, hardly active on COX by itself, is well tolerated by these patients. However, salicylate moiety appears to interfere with aspirin inhibitory action on platelets and vascular COX. Such interaction, if present at the level of respiratory tract, may be of interest to pathogenesis of ASA-induced asthma.

We performed a double-blind, placebo-controlled, randomized cross-over study on the effect of choline magnesium trisalicylate (CMT, trilisate) pre-treatment on ASA-induced adverse reactions in nine patients. Pulmonary function tests, nasal symptoms score, PNIF and serum salicylate levels were monitored following challenges with threshold doses of ASA. Trilisate administered at a dose of 3000 mg daily for 3 days, offered a moderate protection against ASA-induced symptoms; it diminished the severity and/or delayed the appearance of FEV₁ fall. Maximal decreases in FEV₁ as well as reaction intensity indexes were significantly lower ($P < 0.02$ and $P < 0.002$, respectively) after trilisate pre-treatment as compared to placebo. Trilisate also attenuated nasal symptoms in three out of five patients. Although the precise mechanism of the protective action of trilisate is unknown, our data support the possibility of interaction between salicylate and ASA on cyclo-oxygenase locus in the respiratory tract in ASA-intolerant patients.

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Introduction

In some patients with asthma, aspirin (ASA) and other non-steroidal anti-inflammatory drugs (NSAID) precipitate asthmatic attacks. This is a distinct clinical syndrome called aspirin-induced asthma (AIA) [1-3]. The capacity of NSAID to induce asthmatic attacks is closely related to their inhibitory effect on cyclo-oxygenase, the gateway enzyme for the prostaglandin pathway [4]. Sodium salicylate does not inhibit prostaglandin biosynthesis in man [5-7], and is well tolerated by patients with aspirin-induced asthma [1,4].

Though hardly active on cyclo-oxygenase by itself [5,6,8], salicylate moiety appears to interfere with the reaction between aspirin and cyclo-oxygenase. In rats and rabbits it protects platelet cyclo-oxygenase against inhibition by aspirin [9,10]. In rats, it may protect vascular cyclo-oxygenase in a similar fashion [10]. In guinea-pigs, the salicylate prevents the effects of aspirin on arachidonic-induced bronchoconstriction *in vivo* [11]. Recently, Szmidt *et al.* [12] in an open study found that sodium salicylate offered protection against bronchial and nasal symptoms provoked by aspirin in patients with AIA. Such interactions are of interest to pathogenesis of this type of asthma. We therefore evaluated, in a double-blind cross-over study, the effects of choline magnesium trisalicylate (CMT, trilisate) pre-treatment on aspirin-induced symptoms in aspirin-intolerant patients with

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asthma. CMT, a salicylate used in therapy of rheumatoid arthritis [13], is well tolerated by aspirin-sensitive asthmatics [14].

Patients and methods

Nine aspirin-sensitive asthmatics (five women and four men, age range 26–50 yr, mean age 38 yr) were studied (Table 1). Three were on oral or inhaled corticosteroids, the dosage of which was small and remained unaltered during the study. Four patients were on beta-agonists; these were stopped 12 hr before the trial. In two patients who took theophylline regularly this drug was withheld 15 h before the study.

The patients were in a stable clinical condition and the stability of their pulmonary function tests was examined shortly before they entered the proper trial. The procedure consisted of measurements of pulmonary function tests (see Methods) every 30 min for 6 hr following placebo administration. All patients who manifested greater than 10% fall in FEV₁ were not suitable for further studies and challenges.

After being briefed on the study procedure and possible side-effects, each patient signed a consent to confirm willingness to participate in the study. Human Research Committee approval was obtained for all studies.

In all patients the hypersensitivity to aspirin was confirmed by oral challenge tests performed at least 4

weeks before the proper study [1,4]. Individual threshold aspirin doses precipitating at least 15% fall in FEV₁ with clinical symptoms of bronchial obstruction and/or intense rhinorrhoea and nasal blockage were thus established and used in this study. They varied from 30 to 120 mg of ASA, mean value 77 mg, median value 80 mg (Table 1).

Study design

This was a double-blind, placebo-controlled, randomized cross-over study. All patients received as a pre-treatment either placebo or two tablets of trilisate 750 b.i.d. for 3 days and additionally 2 hr before the challenge with individual threshold ASA doses. Each tablet of trilisate 750 (Purdue Frederick, CO, U.S.A.) contains 440 mg of choline salicylate combined with 544 mg of magnesium salicylate, to provide 750 mg salicylate content. Serum levels of salicylate were measured after placebo or salicylate pre-treatment just before the aspirin challenge, using the Quantimetrix Serum Salicylate Assay (Quantimetrix, Hawthorne, CA, U.S.A.).

Clinical observation and pulmonary function tests were monitored for 6 hr following the ASA challenge. The challenges were separated by a period of 2 weeks.

Methods

Pulmonary function tests included FVC, FEV₁, MEF₅ at 25%, 50% and 75% of forced vital capacity. They were recorded on a flow-integrating computerized pneumotachograph (Pneumoscreen, E. Jaeger, W. Germany). Blockade of the nose and watery discharge from the nose were recorded by the patients themselves and rated using a four-point scale (0–3: none, mild, moderate, severe). Peak nasal inspiratory flow (PNIF) was used as an objective index of nasal patency. It was measured with Youlten apparatus at the same time intervals as the pulmonary function tests.

Statistical analysis was performed using the *t*-test for dependent samples. To take into account both the maximal fall in FEV₁ following ASA challenge and the time of its occurrence the index considering these variables was calculated as follows:

$$\text{reaction's intensity index} = \frac{\Delta\text{FEV}_1 \times 100}{t};$$

ΔFEV_1 = maximal percentage fall in FEV₁ as compared to baseline, *t* = time of maximum FEV₁ fall (min) from the beginning of the challenge.

Results

Following aspirin challenge (30–120 mg) seven out of nine patients (nos 1–7) developed symptoms of bronchial

Table 1. Clinical characteristics of nine aspirin-intolerant patients studied

Patient no.	Initials	Sex	Age (yr)	Therapy	ASA threshold (mg)
1	K.M.	M	27	Beclomethasone dipropionate 400 µg	120
2	S.W.*	F	36	Prednisone 7.5 mg Theophylline 750 mg β-mimetics	30
3	S.E.	F	26	Prednisone 7.5 mg Theophylline 750 mg β-mimetics	40
4	W.S.*	M	50	—	120
5	H.K.	M	28	β-mimetics	30
6	J.E.	F	39	—	80
7	S.Z.*	F	40	β-mimetics	40
8	H.T.*	F	48	—	120
9	B.B.*	M	46	—	120

* Subjects in whom nasal symptoms appeared following ASA challenges.

obstruction, while two others (nos 8 and 9) had nasal symptoms only. Pre-treatment with trilisate led to serum salicylate levels ranging from 15.1 to 46.5 mg/100 ml, mean 32.3 mg/100 ml (Table 1).

In seven patients who responded to aspirin with bronchial obstruction, FEV₁ declined from the initial values by 16.5–48.4% (mean 34.9%). In all patients salicylate pre-treatment attenuated the intensity of bronchial reaction to aspirin. In five, the maximal fall in FEV₁ was less pronounced (8.9 and 32.3% (mean 18.8%) from the baseline values); in one subject (no. 2) the lowest levels of spirometric values were the same (48.4 vs. 46.4%) but the reaction occurred 2.5 hr later; and in one asthmatic (no. 1) both the intensity of the bronchospasm and the time of its appearance were significantly inhibited (Table 2). Mean absolute fall in FEV₁ following placebo pre-treatment was 1.11 l (s.d. 0.4) and 0.62 l (s.d. 0.3) for trilisate pre-treatment. Statistical analysis of both absolute and percentage decreases in FEV₁ following ASA challenges showed significant difference ($P < 0.02$ and $P < 0.006$) between the results of placebo vs. trilisate pre-treatments. These differences were even more pronounced when reaction intensity indexes were evaluated ($P < 0.002$). There were no significant differences between baseline FEV₁ values following placebo or trilisate pre-

treatment ($\bar{x} = 3.33$, s.e.m. = 0.37, s.d. = 0.91 vs. $\bar{x} = 3.25$, s.e.m. = 0.28, s.d. = 0.71, $P = 0.49$).

Two patients (nos 8 and 9) exhibited primarily nasal response without a concomitant fall in FEV₁ after aspirin challenge (Tables 2 and 3). In one of them, the reaction was substantially inhibited after salicylate pre-treatment (Fig. 1) while in another it was of the same intensity. This patient also suffered from abdominal pain after aspirin challenge, a phenomenon which was observed several times during previous challenges. The gastric symptoms were absent following trilisate pre-treatment.

Three of the seven asthmatic responders (nos 2, 4 and 7) experienced nasal symptoms as well (Table 3). The reaction was less intense in two of them and in one patient it was almost the same after salicylate pre-treatment. Thus, taken together, in three of five patients who experienced nasal symptoms following aspirin challenge, salicylate pre-treatment attenuated their intensity.

In three patients (nos 2, 3 and 6) salicylate pre-treatment provoked moderate tinnitus and headache, but high serum salicylate levels were recorded in all of them.

Discussion

In our patients, CMT (trilisate) produced moderate protection against aspirin-induced bronchospasm,

Table 2. Intensity of ASA-precipitated bronchial reactions in nine patients studied, challenged with individual threshold doses of aspirin following placebo or trilisate pre-treatment

Initials	ASA challenge following placebo pre-treatment					ASA challenge after trilisate pre-treatment					Serum salicylate following trilisate pre-treatment
	Baseline FEV ₁ (l)	Minimal FEV ₁ after ASA (l)	FEV ₁ (%)	<i>t</i> (min)	RI	Baseline FEV ₁ (l)	After ASA (l)	FEV ₁ (%)	<i>t</i> (min)	RI	
K.M.	4.70	3.11	33.8	240	0.14	4.11	3.82	7.1	330	0.02	32.1
S.W.	2.44	1.26	48.4	150	0.32	2.52	1.35	46.4	300	0.15	46.5
S.E.	2.72	1.47	46.0	225	0.2	2.76	1.87	32.3	270	0.12	42.9
W.S.	3.14	2.37	24.5	150	0.16	3.37	2.92	13.4	240	0.06	30.6
H.K.	4.21	2.55	39.4	300	0.13	4.02	3.09	23.1	300	0.08	15.1
J.E.	2.10	1.35	35.7	240	0.15	2.20	1.83	16.8	300	0.06	35.3
S.Z.	4.00	3.34	16.5	360	0.05	3.80	3.46	8.9	360	0.02	42.9
H.T.	Profound nasal symptoms only*					Mild nasal symptoms only*					
B.B.	Profound nasal symptoms only*					Profound nasal symptoms only*					

* For detailed results see Table 3.

FEV₁, maximal fall in FEV₁ following ASA challenges (% of baseline).

t, time of maximum fall in FEV₁ following ASA challenges (min).

RI, reaction intensity index:

$$\frac{\text{FEV}_1}{\text{baseline FEV}_1} \times 100.$$

$$t$$

Table 3. Nasal symptoms during ASA challenge: peak nasal inspiratory flows (PNIF) measured during ASA-precipitated nasal reactions in five patients challenged with individual threshold doses of aspirin, following placebo or trilisate pre-treatment and the sum of subjective score values recorded by the patients themselves

Patient	Initials	Individual threshold doses of ASA (mg)	Pre-treatment	Baseline	Time after challenge (min)													Sum of the score no. values†
					30	60	90	120	150	180	210	240	270	300	330	360		
2	S.G.	30	Placebo	260	240	135	160	170	120*	110	100	80	70	80	100	140	10	
			Trilisate	260	230	240	280	280	260	280	260	260	280	250	250	250	0	
4	W.S.	120	Placebo	90	90	90	90	50	0*	50	50	70	80	70	70	80	20	
			Trilisate	90	80	90	90	90	50	0	0	0	60	60	70	70	16	
7	S.Z.	40	Placebo	200	220	160	200	210	220	200	180	140	150	130	70	30	18	
			Trilisate	230	220	230	220	220	220	220	220	230	230	220	220	210	0	
8	T.H.	120	Placebo	100	100	40	40	0	0	0	0	0	0	0	0	0	31	
			Trilisate	100	80	80	90	80	90	70	80	80	75	50	75	80	5	
9	B.B.	120	Placebo	220	230	220	200	170	120	50	45	45	50	50	60	60	30	
			Trilisate	200	200	130	50	10	10	0	0	0	10	10	20	20	29	

* Following this measurement the patients received fenoterol (Berotec, Boehringer, Ingelheim, FRG) and/or aminophylline because of dyspnoea (aminophylline 0.25, Polfa, Poland).

† The values represent the sum of individual subjective score values recorded every 30 min throughout the ASA-challenges.

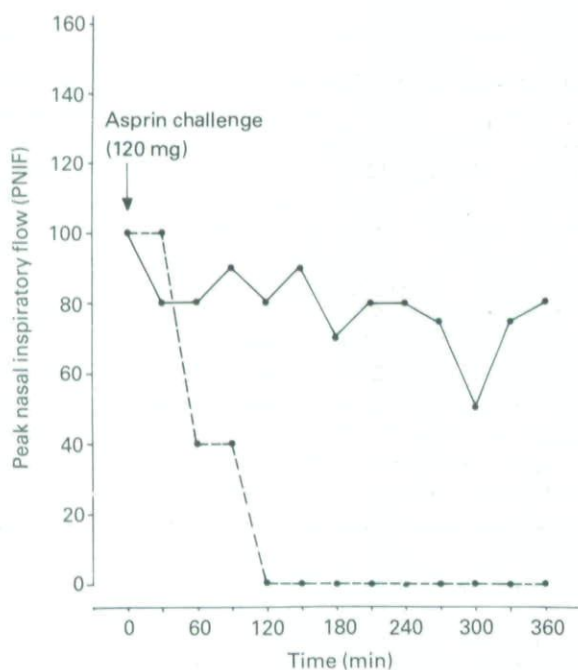


Fig. 1. PNIF values during aspirin challenges following trilisate (●—●—●) or placebo (●---●---●) pre-treatment in patient H.T. (no. 8).

diminished the intensity and/or delayed the onset of FEV₁ fall precipitated by the threshold dose of aspirin. It also prevented nasal symptoms in three of five patients. These results might point to interaction of aspirin and salicylate in the upper and lower respiratory tract of aspirin-sensitive asthmatics. The interaction appears to be competitive and dose-related. Thus, Cerletti *et al.* [15] found that sodium salicylate given to six volunteers at a dose of 1000 mg prevented subsequent inhibition of platelet aggregation by 40 mg of aspirin. Pre-treatment with 250 mg salicylate, caused proportionally smaller prevention of aspirin effect on platelet aggregation. The plasma salicylate levels registered in our patients following trilisate administration were even higher (200–300 µg/ml) than those found to have protective action by Cerletti *et al.* (75 µg/ml) [15]. The results of our study, as well as experimental data in animals [16] and humans [15,17], suggest that high salicylate–aspirin dose ratio must be obtained to demonstrate the salicylate protection against aspirin inhibitory effect on cyclo-oxygenase. The failure of Rosenkranz *et al.* [7] to show any interference of salicylate on antiplatelet efficacy of aspirin in human volunteers might have resulted from different aspirin–salicylate doses administered to the subjects.

The target cell or tissue for aspirin–salicylate interaction in AIA is unknown. It has been postulated that cyclo-oxygenase of mast cell eosinophils, platelets, neutrophils

and macrophages [18–22] may be involved in aspirin-induced syndrome. Our results may provide an additional indirect evidence on the role of cyclo-oxygenase in the pathogenesis of aspirin hypersensitivity.

The protection offered by CMT was not restricted to the tissue of the respiratory tract. Interestingly, in one patient who developed abdominal pain on several previous challenges with threshold dose of aspirin (120 mg) the symptoms did not appear after trilsate pre-treatment. This phenomenon is in agreement with the experimental results published by Ezer *et al.* [23] who found that salicylate diminishes the gastric lesions induced by aspirin and other NSAIDs.

We cannot, however, exclude the possibility that the protective effect of salicylate in AIA might result from pharmacological activities of salicylate other than interference with aspirin [24–26]. Salicylates may exert anti-inflammatory effects by scavenging free radicals [27]. The role of airway inflammation in the pathogenesis of bronchial asthma is well established [28]. In fact, the anti-inflammatory corticosteroids protect aspirin-intolerant asthmatics against aspirin challenge [29]. Moreover, salicylates inhibit the transformation of HPETE to HETE [30], the putative mediators of AIA [18]. The mechanism of the protective effect of salicylate, reported here, remains to be established.

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