

Oral acetylsalicylic acid (aspirin) challenge in asthmatic children

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Summary

Thirty-two asthmatic children, mean age 9.6 years (range: 6-14 years), were studied by oral challenge with acetylsalicylic acid (Aspirin), and their PEFR was recorded at 30 min intervals for 3 hr. They had been asthmatic for a mean of 7.1 years. Other allergic symptoms (urticaria, rhinitis or atopic dermatitis), were present in 81% of the patients, and a family history of atopy in 94%; the mean blood eosinophilia was 590 cells per mm³. In three children aspirin induced a fall in PEFR values less than 8% which was non-significant. In the group as a whole there was an increase in the PEFR values of 13.9%, 150 min after aspirin challenge. These values were subjected to statistical analysis (Kolmogorov-Smirnov, Student's and Wilcoxon tests), which showed this increase to be significant at a level of $P = 0.001$. Possible mechanisms involving prostaglandin synthetase inhibition by aspirin are discussed as an explanation for this increase.

Introduction

Untoward effects due to aspirin were recorded 3 years after its introduction. Samter & Beers (1968), reviewing aspirin effects on asthmatic adults identified the triad of asthma, nasal polyps and aspirin-induced asthma. Later studies showed that the incidence of aspirin-induced asthma in asthmatic adults ranges from 19% (McDonald, Mathison & Stevenson, 1972) or 20% (Farr, 1970) up to 25% (Stenius & Lemola, 1976). Most of these cases were not clinically apparent.

In children, in whom aspirin consumption is equal to that of adults, very few studies have been undertaken; most refer to isolated cases (Yunginger, O'Connell & Logan; 1973; Marcoux & Labbé, 1973). Falliers (1973), reviewing 1298 chronic asthmatic children, found an incidence of 1.9%. Rachelesfky *et al.* (1975), challenging orally with aspirin, found aspirin-induced asthma in 28% of children and Vedanthan *et al.* (1977) found aspirin-induced asthma in 13% of their subjects.

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It is generally assumed that aspirin-induced asthma is very uncommon in children; moreover, cross-sensitivity between aspirin and tartrazine can frequently be seen (Stenius & Lamola, 1976), and these are both widely used by children.

This study was undertaken to discover the possible prevalence of aspirin-induced asthma in a random asthmatic children population.

Materials and methods

Subjects

Thirty-two asthmatic children (eleven females, twenty-one males) who regularly attended the outpatient asthma clinic of the Children's Hospital entered in this study. No selection of the patients was made, and informed consent was obtained for the study. Their ages ranged from 6 to 14 years, with a mean of 9.6 years. They had suffered from asthma for 1 to 13 years, with a mean of 7.1 years. The asthma diagnosis was based on the presence of recurrent reversible airflow obstruction.

Familial history of atopy was found in 94% of the children, and 81% had other allergic symptoms, such as rhinitis, urticaria or atopic dermatitis. Eighteen children had positive weal and flare reactions to intradermal testing with common allergens (house-dust, mites, moulds, pet epithelia and pollens).

The group had received various therapies, which included short term oral or systemic corticosteroids, DSCG, beclomethasone dipropionate, β_2 -agonists such as salbutamol or fenoterol, and aminophylline. Eight children were on regular hypo-sensitization therapy to house-dust or moulds. Mean blood eosinophilia for this group was 590 cells per mm³.

None of them had a previous history of drug allergy or nasal polyps, but sinus X-rays showed decreased aeration of the paranasal sinuses in almost all the children.

Challenges

Corticosteroids, whether systemic, oral or inhaled, were stopped 7 days prior to the challenges. DSCG, β_2 -agonists, aminophylline and antihistamines were stopped 12–24 hr prior to the challenges. On the challenge day, children free from symptoms, without having eaten, had their basal PEF recorded on a Flo-Scope, (Meeda Scientific Instrumentation Ltd, Israel), the highest value of three consecutive readings being taken. They were then given a tablet of 500 mg pure acetylsalicylic acid and allowed to have a light breakfast, with their PEF being checked every 30 min with the highest of three consecutive readings being taken. Simultaneously, a physical examination was made, noting wheezing, rhinorrhea, flushing, ocular congestion or malaise. Readings were taken for up to 3 hr, and the challenge was stopped if a fall of 20% or more (of the basal PEF) or physical signs of bronchial obstruction appeared. These signs were taken as indicative of aspirin-induced asthma.

Four children were re-tested under the same conditions because their PEF curves increased very significantly during the 3 hr period, thus indicating possible acclimatization to the spirometer, and the results of the second test were used if the PEF valve was different from the first.

Statistical analysis

From the data obtained, the values of the basal PEF were compared with the mean values of the 150 and 180 min points (PEF 150–180 min in Table 1). The Kolmogorov

	Sex	Age (years)	Height (cm)	Basal PEFR (l/min)	PEFR at 150-180 min*	Difference	Percentage from Basal PEFR†
(1)	F	6	114.0	140	134.0	-10.0	-7.14
(2)	M	13	141.5	260	272.5	+12.5	+4.81
(3)	M	9	128.0	140	162.5	+22.5	+16.07
(4)	F	7	116.5	150	205.0	+55.0	+36.67
(5)	M	14	148.0	195	200.0	+05.0	+2.56
(6)	M	13	152.0	280	337.5	+57.5	+20.54
(7)	M	10	135.0	145	170.0	+25.0	+17.24
(8)	M	11	142.0	215	207.5	-07.5	-3.49
(9)	M	13	144.0	235	265.0	+30.0	+12.77
(10)	M	10	140.0	220	240.0	+20.0	+9.09
(11)	M	7	123.0	190	205.0	+15.0	+7.89
(12)	F	11	145.0	215	250.0	+35.0	+16.28
(13)	M	12	150.0	255	312.5	+57.5	+22.55
(14)	F	9	135.0	175	207.5	+32.5	+18.57
(15)	F	13	156.0	225	300.0	+75.0	+33.33
(16)	M	8	137.0	190	245.0	+55.0	+28.95
(17)	M	9	132.0	200	207.0	+07.0	+3.50
(18)	M	9	145.0	160	165.0	+05.0	+3.12
(19)	F	11	152.0	330	335.0	+05.0	+1.52
(20)	M	9	140.0	170	250.0	+80.0	+47.06
(21)	M	7	123.0	195	245.0	+50.0	+25.64
(22)	F	10	136.0	240	250.0	+10.0	+4.17
(23)	F	6	112.0	150	150.0	00.0	0.00
(24)	M	9	136.0	255	265.0	+10.0	+3.92
(25)	M	6	109.0	130	140.0	+10.0	+7.69
(26)	F	6	110.0	115	150.0	+35.0	+30.43
(27)	M	9	136.0	150	195.0	+45.0	+30.00
(28)	M	7	118.0	120	150.0	+30.0	+25.00
(29)	F	10	128.0	170	217.5	+47.5	+27.94
(30)	F	13	147.0	390	367.5	-22.5	-5.77
(31)	M	13	156.0	400	405.0	+05.0	+1.25
(32)	M	8	133.0	165	282.5	+117.5	+71.21
Total		308	4320.0	6570	7484.5	914	—
Mean		9.62	135.0	205	233.9	28.58 (s.e. = 5.26)	+13.92%

* PEFR from the mean of the values taken at 150-180 min (l/min).

† Difference in percentages of increase or decrease from basal PEFR values.

rov-Smirnov test was used to check the normal distribution of the difference between the samples; Student's *t*-test was used to test the significance of the differences between the samples and Wilcoxon's *T* test was used to re-check these differences if the sample did not follow a normal distribution.

Results

As shown in Table 1, three children had a fall in their PEFR values of less than 8% (cases Nos 1, 8 and 30).

Sixteen children had an increase in their PEFR ranging from 16% to 71%. Twelve children had an increase of less than 15% and one child showed no change in his PEFR throughout the study.

For the whole group the mean increase in the PEFR was 28.58 l/min (± 5.26), an increase of 13.9% above the mean basal PEFR.

The Kolmogorov-Smirnov test showed that the hypothesis of a normal distribution could be accepted for the PEFR differences data.

Student's test, with $t = 5.05$ ($P < 0.001$), indicate that the mean of the differences (28.58 l/min.), was significantly higher than zero, and Wilcoxon's test, with $T = 29$, ($P < 0.001$), indicated that the positive differences predominated significantly, and showed a higher range compared with the negatives.

None of the cases challenged had to be stopped before the 3 hr period because of excessive aspirin-induced asthma.

Twenty children had PEFR levels below the normal values for their height and age. There was no conclusive relationship between the percentage increase or decrease in the PEFR at the 150–180 min period with the predicted basal PEFR for each child. Similarly, the three children who had a fall in their PEFR values had no special characteristics: two had their values within the normal range and the other one had a basal PEFR value 65% of the predicted.

No other reactions such as rhinorrhea, urticaria, ocular congestion or malaise were noted, and control values 24 hr later were normal.

Discussion

In our group no aspirin-induced asthma was found, and there was a generally statistically significant rise in the PEFR curve. These findings are in contradiction with those of Rachelesfky *et al.* (1975) and Vendanthan *et al.*, (1977). The difference in the results could be due to the ages of the populations sampled, as their group had a mean age significantly higher (13 and 13.5 years) than ours (9.6 years), and their group comprised subjects up to 18 years. It should be noted that the mean age of aspirin-induced asthma in their paper was even higher (13.6 and 14.2 years).

The dose of aspirin used (500 mg) on fasting subjects suggests that good absorption of the drug is to be expected, and the PEFR was recorded for 3 hr because the maximum levels of aspirin in the blood are reached between 30 and 180 min after ingestion. This, and the fact that intermediate values of the PEFR differed little from the 150–180 min values, was the reason for the use of the means of the latter values for the statistical analysis.

It can be argued that the PEFR is not as accurate as a complete study of the whole airways resistance (*Raw*), by whole-body plethysmography, but this technique is very troublesome with children, particularly in the younger age group, and the PEFR

gives similar results to the FEV_1 or the FEF 25–75, both values being used currently in similar studies.

The fact that in our group no aspirin-induced asthma was found can be interpreted from different points of view, especially regarding the overall increases in the PEF values. It stresses the fact that children's asthma can be biologically different from adult asthma with respect to mediators involved, but it may change from one type to another.

Although Samter & Beers (1968) suggested that peripheral analgesics may act at peripheral chemoceptors, and thus initiate a series of reflexes that could be responsible for the bronchial obstruction, and Farr (1970) suggested that repeated ingestion of aspirin could induce an acetylation of different body proteins, preceding the symptomatic triad, it was Stevenson *et al.* (1976) who demonstrated that aspirin challenge in aspirin-induced asthmatics produced a rise in plasma histamine which paralleled the spirographic levels of obstruction. Basomba *et al.* (1976) and Pasargiklian *et al.* (1977), in turn showed that DSCG prevented aspirin-induced asthma.

More conclusive evidence seems to appear when the possible role of the prostaglandins is investigated. Vanselow & Smith (1967) reported that indomethacin, a prostaglandin synthetase inhibitor, could also precipitate bronchial obstruction in asthmatics, and Szczeklik, Gryglewski & Czerniawska-Mysik (1975) showed that aspirin, indomethacin, phenylbutazone, mefenamic acid and flufenamic acid could all precipitate bronchial obstruction in asthmatics with aspirin-induced asthma, all these drugs sharing in common an inhibitor effect on prostaglandin synthetase; whilst salicylamide, paracetamol, benzydamine and chloroquine, although analgesics, did not share the properties mentioned above.

Although recent reports from Arroyave *et al.* (1977) point to a possible role of actuation of the complement system via the alternative pathway, aspirin-induced asthma could be interpreted as Vane (1975) suggests: namely that in aspirin-induced asthmatics it is normally PGE_2 which is released, and its inhibition by aspirin or related drugs would thus produce a relative imbalance, favouring an excess of $PGF_{2\alpha}$, which is a bronchoconstrictor. In our group exactly the reverse could be assumed, explaining thus the overall aspirin-induced increase in the PEF values. More experimental work is needed to confirm these facts.

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