

# Inhibition of exercise-induced asthma by different pharmacological pathways

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**Godfrey, S. and König, P. (1976).** *Thorax*, 31, 137–143. **Inhibition of exercise-induced asthma by different pharmacological pathways.** Exercise-induced asthma (EIA) was provoked by standardized treadmill running for 6 minutes in 15 asthmatic children. The tests were carried out after the administration of a placebo, salbutamol, sodium cromoglycate, choline theophyllinate, and atropine methonitrate aerosol in randomized fashion on different days. The mean post-exercise percent fall in peak expiratory flow rate was 45.2, 4.1, 19.6, 18.3, and 24.9 respectively. The proportion of children having significant amelioration of their EIA compared with those taking the placebo was 100% for salbutamol, 80% for cromoglycate and theophyllinate, and 60% for atropine. Salbutamol, choline theophyllinate, and atropine were bronchodilators at rest whereas cromoglycate was not, and the ability to suppress EIA was unrelated to bronchodilator effect. Even after bronchodilatation at rest, further bronchodilatation occurred during the exercise period.

Exercise of appropriate type and severity provokes a controlled, brief but severe attack of airways obstruction in the asthmatic patient. The maximal response is obtained after some 6 to 8 minutes of running at approximately two-thirds of the aerobic working capacity (Godfrey, Silverman, and Anderson, 1973). Many drugs used to treat asthma have been shown to inhibit exercise-induced asthma (EIA) in various studies or groups of subjects. Thus significant inhibition has been obtained with sympathomimetics, theophylline derivatives, and sodium cromoglycate (Jones, Wharton, and Buston, 1963; McNeill *et al.*, 1966; Davies, 1968; Silverman and Andrea, 1972). On the other hand, no inhibition has been found with antihistamines (Jones *et al.*, 1963) or with steroids in most subjects (König, Jaffe, and Godfrey, 1974). The position of atropine is disputed, some studies in individual patients showing inhibition (Crompton, 1968) but most showing inhibition in only a small proportion of subjects (Jones *et al.*, 1963; Sly *et al.*, 1967; Silverman, 1973). In view of the recent evidence of the role of the vagus in canine and human allergen-induced asthma (Gold, Kessler, and Yu, 1972; Yu, Galant, and Gold, 1972) and the similarity between exercise and antigen-induced asthma as far as the response to sodium cromoglycate or steroids is concerned (König *et al.*, 1974), these results with atropine are perhaps surprising.

Most previous studies of drugs in EIA have not compared different agents in the same subjects, and

the type or form of exercise has varied from study to study. Since this can have such a serious effect on the EIA (Godfrey *et al.*, 1973) and because some of these drugs cause bronchodilatation at rest, we decided to carry out a comparative study in a single group of asthmatic children using a standardized treadmill exercise test.

## SUBJECTS AND METHODS

Studies were carried out on a group of 15 asthmatic children aged 5 to 14 (mean 8.7) years during the course of their routine investigation for which we normally employ exercise tests. Because of the large variability of the response over periods longer than one week (Silverman and Anderson, 1972), the studies were carried out in two separate one-week periods. In the first period, all 15 children were tested with a placebo, salbutamol, choline theophyllinate, and sodium cromoglycate in random order with only one active drug used on any one day. In the second period, seven of the children were retested with placebo and then with atropine on the same day but with a 2-hour gap between tests. We have previously shown that this gap is sufficient to allow a full response in the second test (Godfrey *et al.*, 1973).

All drugs were given in normal therapeutic doses, and these together with the routes of administration of the drugs are shown in Table I. Salbutamol was given from a pressurized aerosol in all but two

TABLE I  
ROUTE OF ADMINISTRATION AND DOSE OF DRUG

Drug	Route and Dose	No. Tested
Placebo	Inhaled lactose powder	13
	Inhaled aerosol propellant	1
	Oral lactose tablet	1
Salbutamol	Pressurized aerosol, 200 µg	13
	Oral tablet, 3-4 mg	2
Choline theophyllinate	Oral tablet, 100-200 mg	15
Sodium cromoglycate	Inhaled powder, 20 mg	15
Atropine	Wet aerosol and face-mask, 0.2% solution, flow rate 9 l/min for 3 min	7

patients to whom it was given by mouth. Choline theophyllinate was given by mouth and sodium cromoglycate by the standard spinhaler device. Atropine was given by nebulization of a 0.2% solution of atropine methonitrate using a Wright's nebulizer for 3 minutes at a flow rate of 9 l/min (modified from Altounyan (1964)). Placebos were given by mouth, resembling salbutamol tablets in one child, by inhaled aerosol propellant in one child, by spinhaler as used for cromoglycate in 13 children, and again by nebulization of saline to simulate atropine in the seven children studied in the second period. Oral drugs were given 2 hours before exercise, and inhaled drugs 5 to 10 minutes before exercise. No other medications were taken for 12 hours before the tests. The studies were carried out in a single-blind fashion by a technician who did not know what result to expect and were analysed by the investigators after completion of the whole series of tests.

The exercise test was carried out on a motor-driven treadmill, as described by Connolly and Godfrey (1970). The child ran continuously for 6 minutes up a gradient of 10% at a speed of approximately 5 kph (3 mph) so as to produce a heart-rate of 170 to 180 beats per minute. The same settings were used for each test in any one child. Peak expiratory flow rate (PEFR) was measured before, every 2 minutes during, and at intervals up to 20 minutes after exercise using a Wright peak flow meter and taking the best of three attempts each time. Normal values were taken from the data of Godfrey, Kamburoff, and Nairn (1970). Results of exercise tests were expressed in terms of the following indices based on the PEFR measured immediately before exercise but after giving the drug or placebo.

$$\% \text{ Rise} = \frac{\text{Highest PEFR during exercise} - \text{Resting PEFR}}{\text{Resting PEFR}} \times 100$$

$$\% \text{ Fall} = \frac{\text{Resting PEFR} - \text{Lowest PEFR after exercise}}{\text{Resting PEFR}} \times 100$$

In addition, these indices were also expressed on a relative scale by converting the PEFR values to the percent of expected before calculating the results (see below).

A preliminary analysis showed no difference in response between inhaled or oral salbutamol, and the data have therefore been treated together. Likewise there was no difference in response to the three forms of placebo, and so the results of the initial set of 15 placebo studies have been used for comparison. A drug result was considered to be significant if the % fall differed by more than 25% from the placebo result because we found this to be the coefficient of variation of the difference of two placebo tests carried out on one day in a group of 80 asthmatic children:

$$\text{Coefficient of variation} = \frac{\text{SD difference between 2 tests}}{\sqrt{2} \times \text{mean}} \times 100$$

Silverman and Anderson (1972), using a different method of calculation based on multiple testing, found a coefficient of variation of 22% for repeated testing within a one-week period.

For comparison between studies, a paired *t* test was used, and differences were considered significant if  $P \leq 0.05$ .

## RESULTS

The individual results of the tests are given in Table II. The values for the resting PEFR before the drugs were given were very similar for all tests, the means lying between 69 and 77% of expected without any significant differences. After the administration of salbutamol, choline theophyllinate, and atropine, there was a significant bronchodilatation with mean rises in PEFR of 18%, 14%, and 18% respectively. In contrast, there were insignificant rises after placebo and sodium cromoglycate of 5% and 2% respectively. These effects on resting PEFR are shown in Figure 1.

The mean results of the exercise tests are shown in Figure 2. There was a significant degree of bronchodilatation during exercise in all tests, which was greatest for the cromoglycate study, but differences were not significant. After exercise with placebo there was a severe degree of bronchoconstriction which was significantly less in the tests following all of the active drugs. The % fall in PEFR after the salbutamol

**TABLE II**  
RESULTS OF EXERCISE TESTS

Patient No.	Placebo		Sodium Cromoglycate		Salbutamol		Choline Theophyllinate		Atropine						
	Resting PEF <sup>1</sup> Before Drug	After Drug	% Rise <sup>2</sup> / % Fall <sup>3</sup>	Resting PEF <sup>1</sup> Before Drug	After Drug	% Rise <sup>2</sup> / % Fall <sup>3</sup>	Resting PEF <sup>1</sup> Before Drug	After Drug	% Rise <sup>2</sup> / % Fall <sup>3</sup>	Resting PEF <sup>1</sup> Before Drug	After Drug	% Rise <sup>2</sup> / % Fall <sup>3</sup>			
1	64	83	24	71	70	25	52	75	100	5	10	16	84	—	—
2	88	82	10	86	88	20	11	78	101	6	1	15	95	—	—
3	66	78	1	83	85	3	20	77	92	0	12	12	105	—	—
4	75	68	0	64	68	0	55	37	56	27	2	5	45	—	—
5	68	65	27	75	75	27	0	72	81	11	2	6	72	4	39
6	65	65	10	74	72	6	0	69	76	12	0	16	65	7	37
7	66	76	15	62	59	31	0	40	96	14	0	17	82	—	—
8	84	94	18	69	82	25	18	69	84	4	0	4	114	8	11
9	106	101	15	111	107	16	4	108	119	4	0	6	114	16	59
10	62	65	17	100	95	17	9	93	116	6	16	6	82	100	0
11	55	59	34	50	51	25	27	58	64	27	2	2	104	92	0
12	50	73	19	47	50	12	40	40	72	6	0	7	57	75	0
13	50	91	0	68	84	18	22	71	89	17	5	10	54	—	—
14	58	74	0	82	85	37	28	81	89	8	2	19	84	—	—
15	70	75	16	52	53	37	28	53	74	14	4	15	60	—	—
Mean	70.3	75.2	16.0	73.9	73.5	18.4	19.6	68.9	87.1	10.1	4.1	12.0	69.6	77.4	24.9
SE	3.9	3.7	3.1	4.4	4.1	2.7	4.7	5.3	4.7	2.2	1.3	1.7	4.8	6.1	8.4

<sup>1</sup> Resting PEF as a percentage of expected normal.

<sup>2</sup> % Rise in PEF as a percentage of resting PEF after drug.

<sup>3</sup> % Fall = fall in PEF as a percentage of resting PEF after drug.

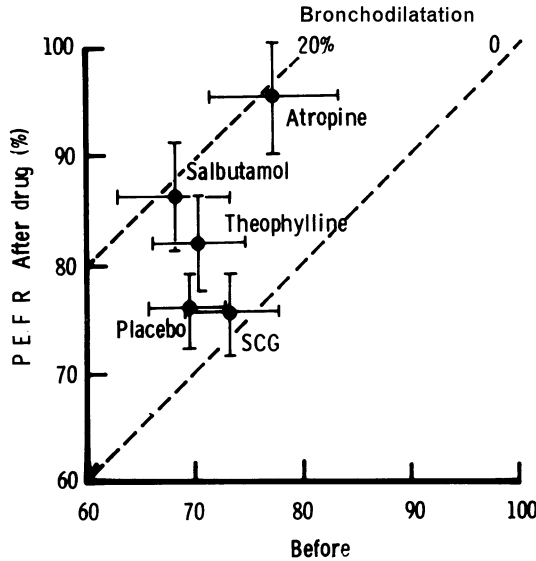


FIG. 1. Peak expiratory flow rate (PEFR) before inhaling the drugs is plotted against PEFR after inhaling the drugs, all measurements being made at rest before the start of the exercise test. The points indicate the mean value for the group of subjects and the bars indicate  $\pm 1$  SEM. SCG = sodium cromoglycate.

exercise test was significantly less than that with the other three active drugs, which did not differ from each other. The blocking effect was calculated as follows:

$$\text{Block \%} = \frac{\% \text{ Fall on placebo} - \% \text{ Fall on drug}}{\% \text{ Fall on placebo}} \times 100$$

Using this index, the mean block was 92% for salbutamol, 58% for choline theophyllinate, 60% for sodium cromoglycate, and 45% for atropine. Again, salbutamol was significantly more effective than the other drugs, which did not differ from each other.

Because of the initial bronchodilatation with some drugs, the results have also been expressed on a scale of PEFR as % expected, as shown in Figure 3. The bronchodilatation due to the drug is indicated by the arrow which shows the rise in PEFR at rest after the drug has been given. The bars then show the subsequent bronchodilatation during exercise and bronchoconstriction after stopping. When analysed in this way, the conclusions are just the same as those above, the post-exercise fall in PEFR being 35% for placebo, 4% for salbutamol, 14% for choline theophyllinate, 14% for sodium cromoglycate, and 23% for atropine. This format shows the impressive bronchodilatation seen during exercise, particularly in the atropine tests when the mean level rose to 106% of expected normal.

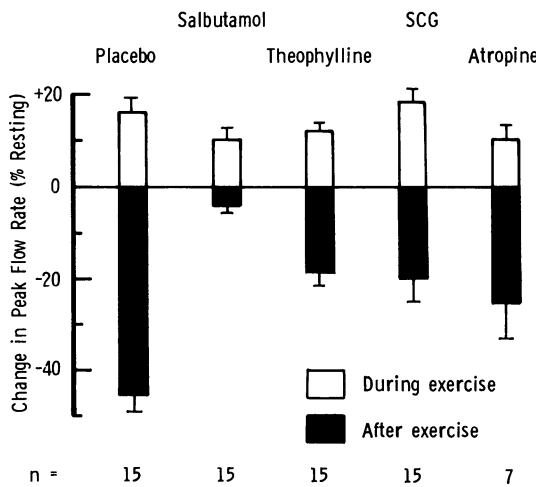


FIG. 2. Bronchodilatation during exercise and bronchoconstriction after exercise expressed as % change from the resting value immediately before exercise but after receiving the drugs indicated. The bars show  $\pm 1$  SEM.

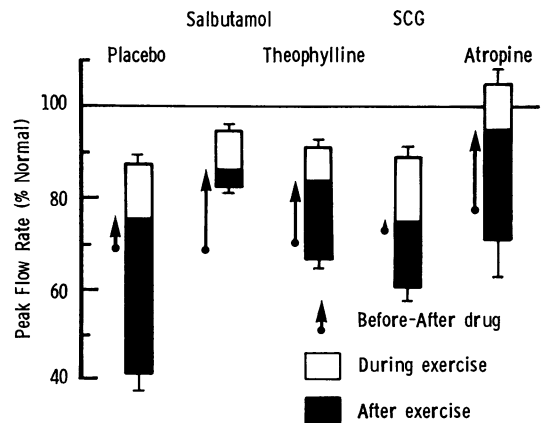


FIG. 3. Same data as in Fig. 2 but expressed on a scale showing the peak flow rate as a % of the expected value. The arrows indicate the change occurring at rest before exercise as a result of giving the drugs indicated. The subsequent bronchodilatation during exercise and bronchoconstriction after exercise are shown relative to the peak flow rate after the drug.

TABLE III  
INDIVIDUAL SIGNIFICANCE OF RESPONSES

Subject	Sodium Cromoglycate	Salbutamol	Choline Theophyllinate	Atropine
1	O	++	++	
2	++	++	++	
3	++	++	++	
4	O	++	O	+
5	++	++	O	O
6	++	++	+	
7	++	++	++	++
8	++	++	++	
9	++	++	++	O
10	++	++	++	++
11	++	++	++	++
12	O	++	++	
13	++	++	++	
14	++	++	++	O
15	++	++	O	

% Fall after drug test:

O not more than 25% less than after placebo.

+ 25 to 50% less than after placebo.

++ more than 50% less than after placebo.

The degree of protection from EIA has also been assessed for each individual patient (Table III). The block was considered as insignificant (O) if it was less than 25% (the coefficient of variation – see methods), as moderate (+) if it was between 25 and 50%, and good (++) if it was more than 50%. It was found that with salbutamol the block was good in all children, and with choline theophyllinate it was good in 10 children, moderate in two children, and insignificant in the other three; with sodium cromoglycate it was good in 11, moderate in one, and insignificant in the other three. As far as atropine was concerned, only four of the seven children had significant blocks, which were good in three and moderate in the other one. Thus, although the mean protection by atropine was significant (% fall less than in placebo test) this was really due to the good effect in only four of seven (60%) of the children.

There was no significant correlation between the degree of bronchodilatation produced at rest and the magnitude of the block of EIA by any of the drugs.

#### DISCUSSION

This study has shown that EIA may be largely prevented by premedication with drugs which act through different pathways, but also that the response to some drugs varies between subjects. We have confirmed the efficacy of a sympathomimetic agent (salbutamol) in preventing EIA and the relatively good effects of a phosphodiesterase inhibitor (choline theophyllinate) and sodium cromoglycate as reported by others (Jones *et al.*, 1963; McNeill *et al.*, 1966; Davies, 1968; Eggleston *et al.*, 1972; Silverman and Andrea, 1972). We gave these drugs in the normal therapeutic doses, and on this basis it appears that salbutamol was most effective and theophylline and

sodium cromoglycate about the same as each other.

On a superficial level it also appears that atropine blocks EIA since the mean percent fall in PEFR was less after the drug run than after the placebo run. However, when the individual studies are analysed, it can be seen that only four of the seven children had significant protection (Table III), and in the remaining three children the difference between tests was no greater than between two placebo tests.

This emphasizes the extreme caution needed when studying drug effects on EIA and shows the importance of considering the inherent variability of a test. Moreover, since placebos themselves have been shown to reduce EIA significantly in up to 40% of children (Godfrey and Silverman, 1973), it is essential to compare the drug test with a placebo test and not merely with a different drug test as both drugs might be acting merely through a placebo effect. Because of these factors it is essential that the form of exercise test should produce a large response and a clear-cut effect, and that it should be as reproducible as possible. We have previously pointed out that this is best achieved by standardized running in the manner described, while other types of exercise, such as walking or cycling, and other patterns of exercise, such as progressively increasing or prolonged work, are much less reliable (Anderson, Connolly, and Godfrey, 1971; Silverman and Anderson, 1972; Godfrey *et al.*, 1973). Failure to allow for these factors probably accounts for some of the confusion over the effects of drugs on EIA. Thus Poppius and Salorinne (1973) failed to demonstrate inhibition of EIA by salbutamol but gave no control or placebo data and used progressive ergometer exercise. Their findings are totally at variance with the results of the present study and with almost every other published study on the effect of sympathomimetics.

We have shown that the inhibition of EIA is unrelated to bronchodilator activity at rest so that sodium cromoglycate had no resting effect on PEFR while the other drugs caused significant bronchodilatation and yet sodium cromoglycate was as effective on EIA as theophylline. Equally when considering the bronchodilators, there was no correlation between this effect and their power to block EIA. If a drug possesses bronchodilator activity, it is impossible to define its site of action in EIA, but sodium cromoglycate must clearly act in a different way from the other drugs and is effective only in preventing induced asthma. Much attention has recently been paid to the vagus, and it has been suggested that antigen-induced asthma, histamine-induced asthma, and possibly other types of asthma may have a final common pathway through a vagal reflex (Altounyan, 1964; Booi-Noord *et al.*, 1970;

Yu *et al.*, 1972). It seems inherently unlikely that this could be true for EIA since our study has shown a significant atropine block in only about 60% of children, despite using a dose which caused bronchodilatation in every case (doubling the specific airways conductance which we measured plethysmographically) and raising the resting heart-rate by a mean of 12 beats per minute. Our results with inhaled atropine agree with those obtained using intravenous atropine (Jones *et al.*, 1963; McNeill *et al.*, 1966; Silverman, 1973), subcutaneous atropine (Sly *et al.*, 1967), or inhaled anticholinergic drug (Poppius, Salorinne, and Viljanen, 1972). It is possible that the PEFR measurement is not sensitive enough to detect small changes in airways calibre and hence some beneficial effect of atropine may have been missed. However, Benatar and König (1974) have shown excellent agreement between the PEFR indices of EIA and changes in the flow-volume curve, while Fisher *et al.* (1970) were unable to detect any benefit of atropine on EIA using a whole-body plethysmograph.

Finally, it is worth noting the bronchodilatation which occurs during the course of the exercise period. This was proportionately greater in the placebo and sodium cromoglycate tests (Fig. 2) but the other drugs were bronchodilators and had raised the resting PEFR before exercise to a point where there was less potential for further rise (Fig. 3). On this basis all four drugs and placebo gave a similar rise during exercise of 8% to 13%. Even so, in the atropine exercise test the PEFR rose above the expected normal value despite the fact that atropine was no better bronchodilator at rest than salbutamol or theophylline. This suggests that vagal tone might still be operating during exercise in the presence of salbutamol, theophylline, or sodium cromoglycate but is inhibited by atropine.

In conclusion we have shown that exercise-induced asthma is normally blocked in all children by salbutamol, in 80% of children by choline theophyllinate or sodium cromoglycate, but in only some 60% of children by atropine.

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