

Pretreatment of Exercise-Induced Asthma in Adults with Aerosols and Pulverized Tablets

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Eighteen adult asthmatics took part in a double-blind crossover study comparing the effect on exercise-induced asthma (EIA) of pretreatment with aerosolized 1) disodium cromoglycate (DSCG), 2) ipratropium bromide (IPTB), 3) fenoterol, 4) DSCG + IPTB and 5) saline.

EIA was completely blocked by pretreatment with the β_2 -agonist, fenoterol. The protective effect of nebulized DSCG and IPTB given alone could not be distinguished from that of isotonic saline. The combination of DSCG and IPTB reduced the post-exercise bronchoconstriction more than any of the two drugs given separately.

Thirteen of the 18 patients went on to a double-blind cross-over study of the effect on EIA of pretreatment with the usually recommended dosages of salbutamol, theophylline and their combination administered as pulverized tablets.

Seven patients were withdrawn from this part of the study because of side-effects, and in the remaining six none of the oral pretreatments could be distinguished from placebo, despite serum theophylline concentrations within or above the commonly recommended therapeutical range.

Key words: aerosols, exercise-induced asthma (EIA)

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It is well documented that running exercise provokes disabling bronchoconstriction in 60–90% of asthmatic children and adults (4, 9, 16). Such bronchoconstriction represents a major obstacle in the clinical management of asthma, and the phenomenon has often been advocated as a reference model to use when testing the efficacy of anti-asthmatic drugs (2, 4, 5, 10, 13).

Traditionally, the principal way of dispensing bronchodilating medication to asthmatics in most countries is in the form of tablets, although the bulk of evidence shows the inhaled route to be preferable, if the above mentioned reference model is being used.

We decided to conduct a study which would allow us at the same time 1) to compare the efficacy of different pretreatments given as inhalation, 2) to compare the effect of an anticholinergic drug and disodium chromo-

glycate given separately and in combination, and 3) to evaluate the relevance of the usually recommended dosages of oral theophylline and salbutamol, alone and in combination, as prophylaxis against EIA.

PATIENTS AND METHODS

Patients

Eighteen adult asthmatics, 11 females and seven males participated in the inhalation study. Their mean age was 30.5 years, s.d. 7.6 years, range 17 to 40 years. All patients had shown EIA in a study concerning the incidence of EIA in adults. They represented asthmatics referred to the Clinic of Allergology at Rigshospitalet, Copenhagen. The average length of asthma history was 60.6 months, range 6 months to 22 years.

Seventeen of the participating 18 patients had one or more allergies. Twelve patients had positive skin tests, nine rhinitis. Twelve had blood eosinophilia (> 350 mill/l) and eight had elevated IgE (> 263 U/ml). Within 6 months prior to the study all patients had undergone pulmonary function test including measurements of static lung volumes, ventilatory capacity and transfer factor for CO. Six patients had lung function within the normal range, and the remaining 12 had decreased maximal expiratory flows that were normalized after inhalation of 0.16 mg of isoproterenol. All patients had normal heart rate function measured by electrocardiography, and normal findings on chest X-ray. Ten patients were lifelong non-smokers, and three patients smoked less than five cigarettes per day. None of the patients were taking steroids orally.

The effect of pulverized tablets as pretreatment on 13 of the above described patients was also studied.

Methods

EIA-test. Free run was performed in three periods of 2 min each, with a 1-min intermission. After 2 min of running all patients had a pulse of over 160 beats per min. PEFR were measured before exercise, during the intermissions and 0, 2, 4, 6, 8, 13 and 18 min after exercise. Exercise was done at the same time each day.

Pretreatment with aerosols. a) 2 ml (20 mg) disodium cromoglycate (DSCG) plus 2 ml isotonic saline, b) 2 ml (2 mg) fenoterol plus 2 ml isotonic saline, c) 2 ml (0.5 mg) ipratropium bromide (IPTB) plus 2 ml isotonic saline, d) 2 ml (20 mg) DSCG plus 2 ml (0.5 mg) IPTB and e) 4 ml isotonic saline.

These five solutions were given randomized from a Bird MK 7 ventilator equipped with a micronebulizer, which delivers particles from $0.5 \mu\text{m}$ to $4 \mu\text{m}$. The inspiratory flow was kept at 15 l/min, while trigger sensitivity and inspiratory pressure were individualized, but

kept constant for each patient from day to day. The solutions were inhaled from 45–30 min before the exercise. The aerosols were inhaled with tidal breathing. Both DSCG and IPTB administered thus should give optimal effect (1, 8, 15).

Oral pretreatment. All medicine was administered as pulverized tablets. The medicine tested was taken 3 times daily 22, 11, and 1 h before the exercise test. The medicine used was: a) salbutamol $4 \text{ mg} \times 3$; b) theophylline 20 mg/kg/day to the nearest 125 mg, divided into 3 doses; c) a plus b and d) placebo. Blood samples to determine the serum theophylline level were drawn on each day immediately after the exercise. This was 1 h and 10 min after the last dose of tablets had been taken.

Other medicine. No other medicine than the tested was taken during the last 24 h before the exercise.

Study design. Pretreatment with aerosols was given on 5 consecutive days. Oral pretreatment was given on 4 consecutive days during another period which was separated from the inhalation period by an interval of 2 days.

Impairment of lung function after exercise. This was calculated comparing the lowest PEFR after exercise with the highest PEFR immediately before or after exercise (e.g. PEFR immediately before exercise 400. PEFR immediately after exercise 450. The lowest PEFR after exercise 350. Result: $(450-350)/450 = 22\%$).

Serum theophylline assay. High performance liquid chromatography was used to determine serum theophylline (12).

Statistics. Two-way analysis of variance was used to test for differences between the different pretreatments.

Variation in base-line values of 18 subjects on 6 test days.

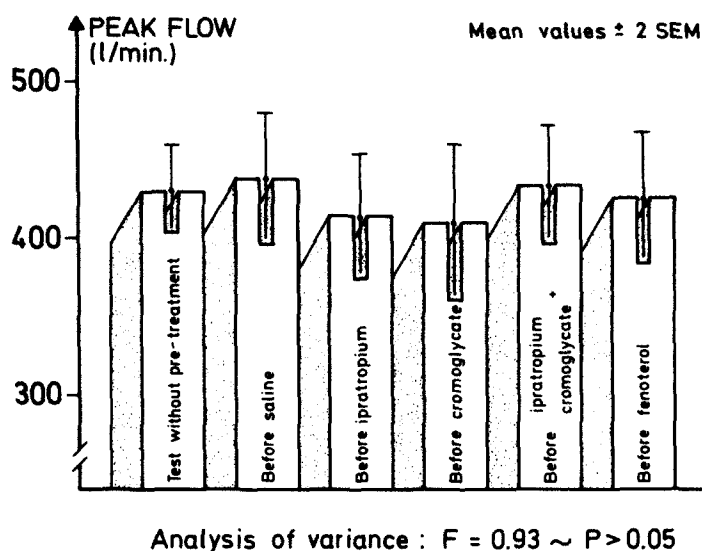


Fig. 1. *Aerosol study.* Variation in base-line values before inhalation. 18 patients on 6 test days. There was very little variation from day to day before the different pretreatments.

RESULTS

During the 5 plus 4 days in the course of which the patients were tested, their individual clinical state remained unchanged.

Aerosol pretreatment

Individual baseline values on the days where the patients were tested with aerosols varied only negligibly (Fig. 1). Figure 2 shows the results of the exercise test after each of the five aerosolized pretreatments had been given. Bronchoconstriction was completely prevented when fenoterol was given. Pretreatment with saline was just as good as pretreatment with DSCG and IPTB when these drugs were given alone. However, when DSCG and IPTB were combined they seemed to have some effect. Comparing bronchoconstriction statistically showed significant differences between the pretreatments ($P < 0.01$).

Three out of 18 patients developed significant EIA after 2 plus 2 min of running, and consequently these three patients ran only 4 min during their test.

The graph in Fig. 2, representing data from the exercise test without pretreatment, shows that any pretreatment might be better than none. The decrease in PEFR after exercise in per cent is shown in Fig. 3.

After pretreatment with IPTB and DSCG none of the patients complained of side-effects, whereas six patients reported distress, and another four had obvious tremor after inhalation of 2 mg fenoterol.

Oral pretreatment

Thirteen patients were given oral pretreatment with pulverized tablets. Six of these completed the study. Serum theophylline was controlled every day (Table 1). Four patients dropped out as they stopped taking their tablets due to side-effects. One patient dropped out because the test had to be stopped every day due to a fall of PEFR of more than

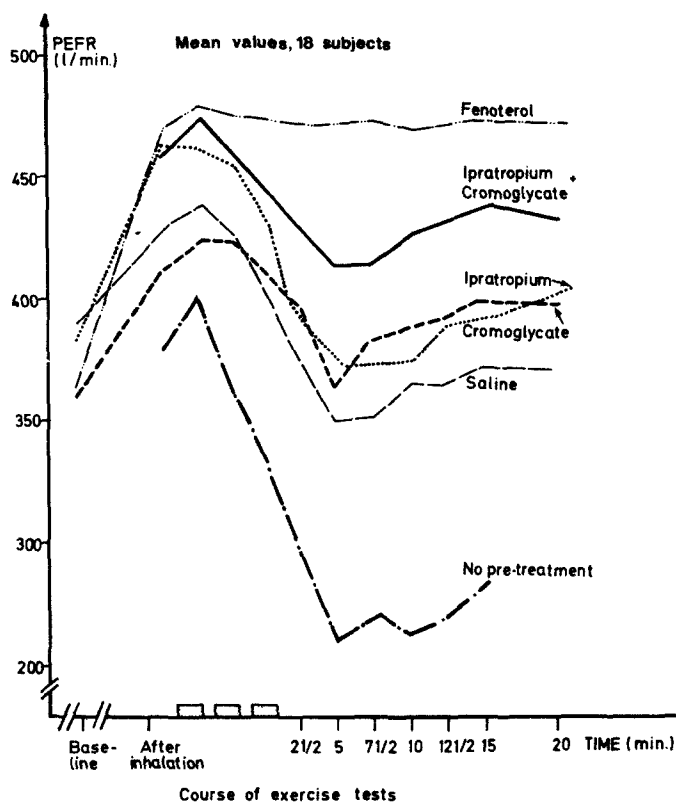


Fig 2. *Aerosol study.* Course of exercise tests, mean values for 18 patients after the five pretreatments and after no pretreatment. Fenoterol completely prevented fall in PEFR after exercise. Pretreatment with saline was just as effective as pretreatment with cromoglycate or ipratropium.

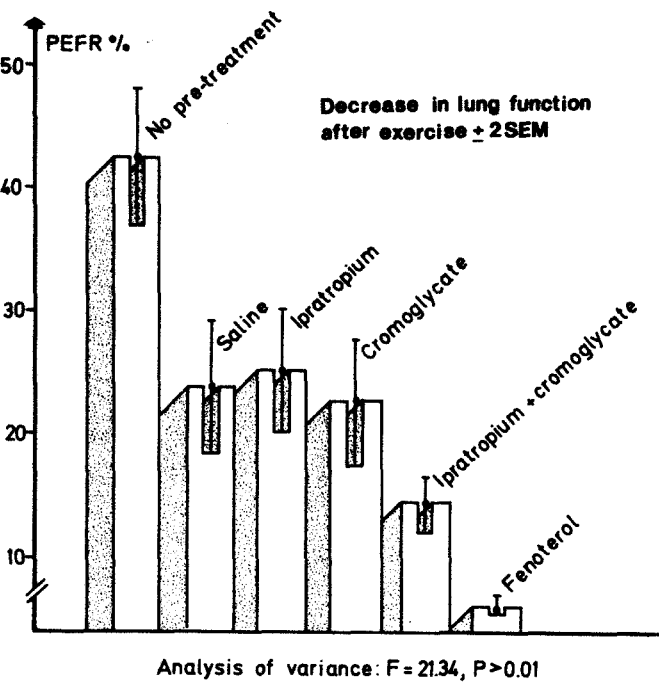


Fig. 3. *Aerosol study.* Decrease in lung function after exercise. The lowest PEFR after exercise is compared with the highest PEFR before, during or immediately after exercise.

40° during the exercise. The decrease in pulmonary function was brought under control with salbutamol spray.

Patient No. 8 had serum theophylline under 10 $\mu\text{g/ml}$ on both days he received theophylline. Patient No. 9 had serum theophylline under 10 $\mu\text{g/ml}$ on the day he received theophylline plus salbutamol. As only the patients who had serum theophylline over 10 $\mu\text{g/ml}$ on the days pretreated with

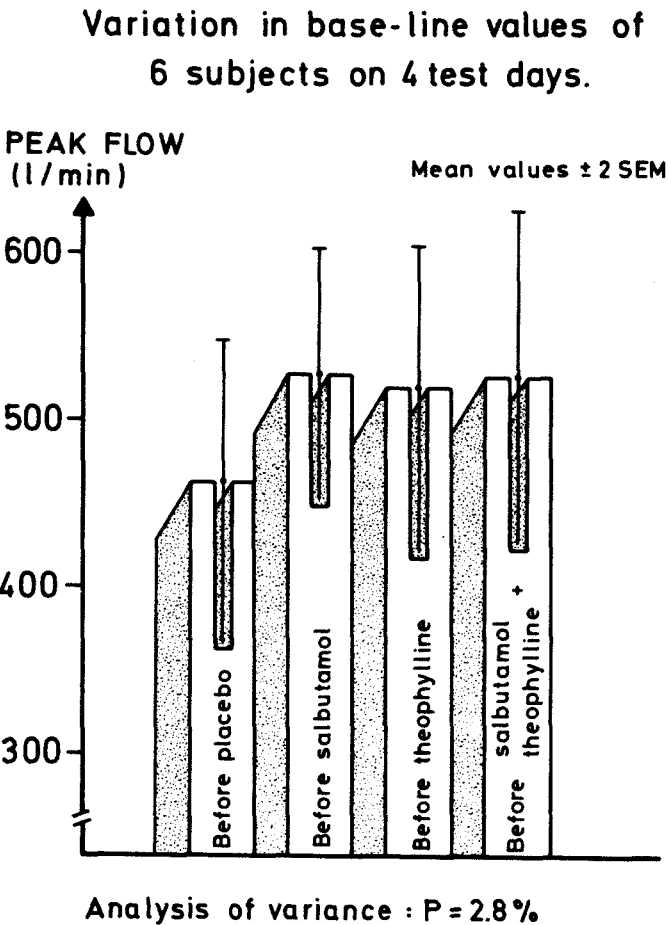


Fig. 4. *Tablet study.* Variation in base-line values before exercise test of six patients on 4 test days. Pretreatment with salbutamol and/or theophylline gave higher base-line values than pretreatment with placebo.

theophylline were included in the study, these two patients were excluded.

Patients No. 1, 4 and 6 had serum theophylline of 4, 7 $\mu\text{g/ml}$, 8, 6 $\mu\text{g/ml}$, and 6, 4 $\mu\text{g/ml}$ respectively on days where they received no theophylline as pretreatment. Patients were

Table 1
Serum theophylline concentrations ($\mu\text{g/ml}$) from nine patients taking all four oral premedications

Patient No.	Pretreatment			
	Placebo	Salbutamol	Theophylline	Salbutamol + Theophylline
1	4	7	18	22
2	3	2	20	18
3	0	0	19	19
4	8	6	25	23
5	0	1	16	11
6	6	4	28	16
7	0	2	12	13
8	0	2	9	6
9	8	2	28	3

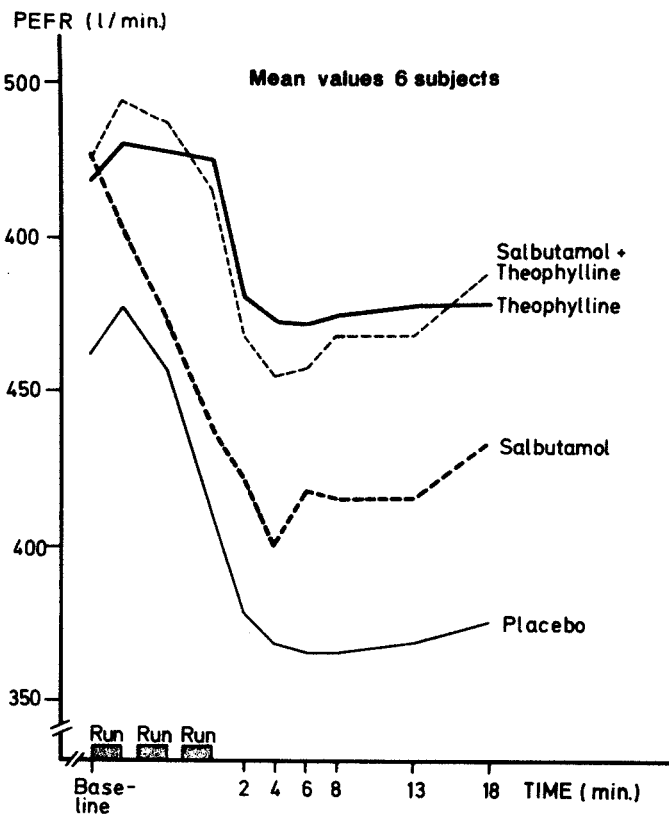


Fig. 5. *Tablet study.* Course of exercise tests, mean values for six patients after four oral pretreatments. With this small number of patients no difference in EIA was seen.

allowed to drink coffee during the study period.

Comparison of the base-line values on the different test days showed a significant difference ($P=0.028$, Fig. 4). Figure 5 shows the course of the exercise test after the different oral pretreatments.

Comparison of the bronchoconstriction after exercise showed no statistical significance on the 5% level ($P=0.1$, Fig. 6).

Side-effects

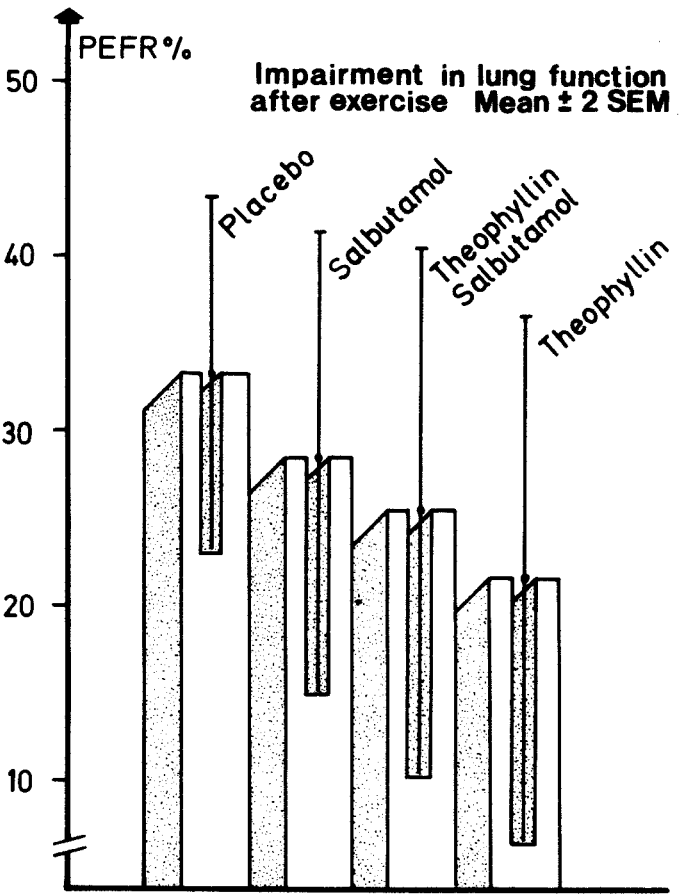
Side-effects were present in three out of 12 patients taking placebo, in five out of 11 taking salbutamol, in seven out of 11 taking theophylline, and in 10 out of 13 taking combined theophylline and salbutamol. Gastrointestinal complaints were registered particularly with theophylline. Other side-effects were sweating, tremor, increased heart rate and headache (Table 2). Twelve out of 13 experienced side-effects on one or more days. One patient did not take the last two placebo

tablets because the first tablet had given her headache, sweating and tremor. It was not controlled as to whether or not she was intolerant to the lactose in the placebo tablet.

DISCUSSION

Aerosol study

We confirmed what has been found in other studies (6, 13, 18), that β_2 -stimulating medication is the treatment of choice against EIA. Many studies have shown that DSCG offers some degree of protection against EIA (6, 8, 17). In our study the protection after pretreatment with DSCG could not be statistically distinguished from that of saline inhalation. When judging this it must be taken into account that with the inhalation technique used less than 20% of the total dose



Analysis of variance: $P > 0.1$

Fig. 6. *Tablet study.* The impairment in lung function after exercise. The lowest PEFR after exercise is compared with the highest PEFR before, during or immediately after exercise.

Table 2

Side-effects after oral premedication

	Placebo	Salbutamol	Theophylline	Salbutamol + Theophylline
Headache		2	1	4
Nausea			1	4
Vomiting	1		3	2
Abdominal pain			2	1
Diarrhoea		1	1	
Tremor	3	3		4
Increased heart rate	2		2	4
Sweating	1			1
No. patients	12	11	11	13

reaches the lungs. The protection might have been better if a higher dose had been used.

Some studies have shown an effect of anticholinergic drugs (6, 11, 17, 18). We were not able to distinguish the effect of IPTB from that of saline, although a very high dose was used. The combined effect of DSCG and IPTB, which reached statistical significance, suggests that each of the drugs might have an effect of their own, which by chance was not demonstrated in this study.

Tablet study

The number of patients completing this part of the study was very small due to side-effects. This was to be anticipated as high doses of theophylline and salbutamol were used to secure therapeutical serum levels of theophylline and maximal effect of salbutamol.

The design with 4 consecutive test days was chosen to minimize day to day variation in EIA (7, 14). This, however implicated that some of the patients on placebo days had high serum theophylline concentrations, which could have favoured the placebo response and thus blurred the comparisons between active drugs and placebo. From a clinical point of view, however, this is of minor importance as none of the drugs or their combinations

protected against EIA to any significant degree when the reported side-effects are considered. Although a statistically significance was not seen between the pretreatments, it could be argued from the figures that theophylline might have some effect.

Conclusion

The present study confirms that oral pretreatment with β_2 -agonists and theophylline are of limited value in the treatment of EIA, and that the drug of choice should be β_2 -agonist delivered through a nebulizer.

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