

Prevention of exercise-induced asthma by drugs inhaled from metered aerosols

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The capacity of salbutamol 0.3 mg (SAL), disodium cromoglycate 3 mg (DSCG), a combination (SAL + DSCG), and ipratropium bromide 80 µg (IB), all given as metered aerosols to prevent exercise-induced (EIA), was compared with that of a placebo, a peroral lactose pill. Seven children participated, having reproducible EIA provoked by running on a treadmill at a heart rate of 170 sustained for 6 min. FEV₁ and volume of trapped gas (VTG), defined as the air volume released during rebreathing oxygen with maximum breaths at the end of a multiple breath nitrogen wash out, were used as tests of spasm in large and small airways. SAL and SAL + DSCG offered complete protection in large and small airways. DSCG and IB prevented EIA in large airways (FEV₁) to 95 %, but only to about 50 % in small airways (VTG). SAL or SAL + DSCG gave significantly better protection (FEV₁ and VTG) than DSCG and IB ($P < 0.01$). Differences between DSCG and IB were not statistically significant. DSCG or propellant caused significant irritation and spasm in small airways (VTG) before exercise. Most subjects seemed to obtain satisfactory protection against EIA by β_2 -agonists.

Key words: albuterol; asthma; disodium cromoglycate; drug therapy; exercise-induced bronchospasm; ipratropium bromide; salbutamol.

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Exercise-induced asthma (EIA) is a major problem especially for young patients (3, 6, 14). The most convenient way to administer drugs for the prevention of EIA is by metered aerosols (9). Different authors claim superiority for different drugs. According to recent recommendations by the Swedish Health Authorities, one author considers disodium cromoglycate to be the superior drug (8) while another author (5) considers that β_2 -agonists are superior. For this reason we have compared the effect on EIA of drugs commercially available as metered aerosols but with different pharmacological actions, in a group of seven children with reproducible EIA. We tested the degree of EIA after placebo (a lactose pill), a β_2 -agonist (salbutamol), disodium cromoglycate, a combination of these drugs, and ipratropium bromide. The degree of EIA was evaluated by the commonly used forced expiratory volume in the first second

(FEV₁), and also by the volume of trapped gas (VTG), which has been shown sensitive to minimum EIA (1, 14) for evaluating abnormality in large and small airways (4), respectively.

MATERIAL AND METHODS

Seven children, 4 boys and 3 girls, 7-16 years of age, with a clinical diagnosis of bronchial asthma since the age of 2 to 4 years volunteered to participate. Both they and their parents gave informed consent to the study which was passed by the Board of Ethics of the University of Lund. The anthropometric data, including predicted normal values for FEV₁ and VTG, are given in Table 1. All children had previously undergone exercise tests on two or more occasions and had a reproducible EIA. On these occasions FEV₁ before exercise did not vary more than 200 ml and VTG not

more than 20 ml from the mean in the same subject. The only medication used was β_2 -agonists and the subjects were free from medication 12 h before the tests. As metered aerosol propellants have been shown to cause bronchoconstriction (18), a lactose pill was given as a peroral "new antiasthmatic" in the placebo experiments. After 20 min a multiple breath nitrogen wash-out (Ohio 700 Nitrogen Analyzer, Ohio Medical Products, Houston, Texas USA) was performed followed by VTG measurement (4, 13). This was done, when the N_2 -concentration in alveolar gas had reached 2%, by rebreathing a vital capacity of oxygen five times into a small bag and measuring the increase in nitrogen concentration in the bag/lung system at the end of the rebreathing period. VTG is defined as the volume of nitrogen released by the rebreathing, expressed as air (13). It has high repeatability and increases significantly also with subclinical bronchospasm (1, 4). FEV_1 was measured with a high fidelity water-sealed spirometer. Using a treadmill, the child ran for 6 min, with a minimum heart rate of 170/min for the last 3 min. The elevation of the treadmill was 5° and the speed adjusted to give the same heart rate on each occasion (14). The lung function tests were repeated 5 min after exercise during maximum EIA.

The order of the different drug experiments was determined by blind selection. All experiments began by measuring FEV_1 and VTG in a basal state. The drug was then inhaled from

a metered aerosol and large spacer (Nebulator®, Draco, Sweden, or Volumatic®, Glaxo, England). With suitable adapters the same spacer could be used for all drugs in all experiments on each child. The drug dispensers were covered with white tape, so the children were unaware of which drug was being used. On different days we tested the effect of 0.3 mg salbutamol (SAL) (Ventoline®, Glaxo), disodium cromoglycate (DSCG) 3 mg, (Lomudal®, Fisons), the combination SAL and DSCG, and ipratropium bromide, (IB), 80 ug (Atrovent®, Boehringer-Ingelheim). The effect of the medication on the basal asthma was measured 15 min after the inhalation of the last puff and was directly followed by the exercise provocation. In the experiments with IB these measurements were postponed to 1 h after inhalation when the drug is said to have maximum effect (16). In two subjects the experiment was repeated on another day with measurements after 15 min. In the placebo experiments SAL was inhaled after the lung function tests following exercise and the effect measured 15 min later.

The experiments were postponed if the child had an infection or spontaneous deterioration of their basal asthma. In subjects with seasonal asthma no tests were done during their period of deterioration.

Statistics. Student's t-test on paired observations was used. A *P*-value of < 0.05 was considered statistically significant.

Table 1

Anthropometric data and predicted forced expiratory volume in the first second (FEV_1) and volume of trapped gas (VTG) of the children in the study

Sex	Age (years)	Height (cm)	Weight (kg)	FEV_1 pred l	VTG pred (ml)	Allergy
M	16	171	64	3.46	92	pollen, house mites
M	15	166	49	3.20	84	animals, moulds
M	13	152	45	2.48	81	pollen, house mites
M	8	136	32	1.80	60	animals
F	16	174	60	3.91	97	pollen, moulds
F	16	168	54	3.62	70	house mites
F	13	160	61	2.88	84	animals, pollen
Mean	13.9	161	50.7	3.05	81	

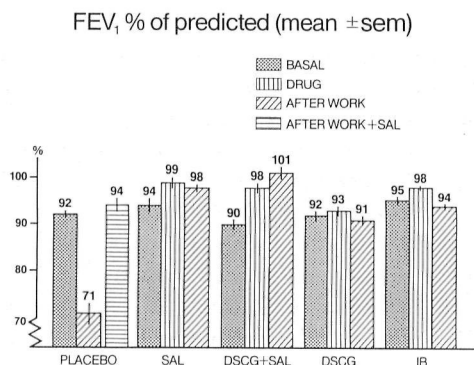


Fig. 1. Forced expiratory volume in the first second (FEV₁) in per cent of predicted normal value in the various experiments. Placebo: premedication with a lactose pill; SAL: premedication with salbutamol; DSCG: after disodium cromoglycate; SAL + DSCG: after combination; IB: after ipratropium bromide. The bars denoted "after work" show changes after work or degree of exercise-induced asthma.

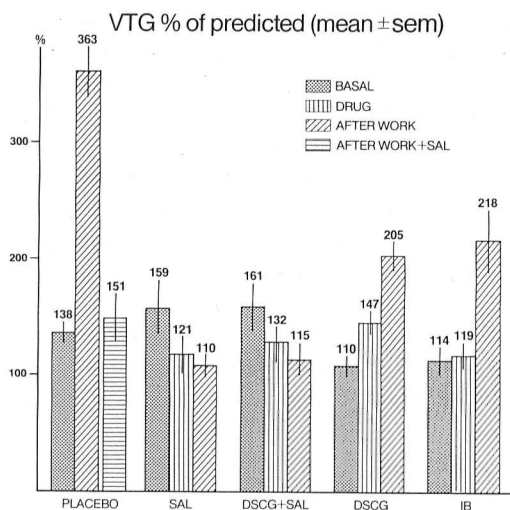


Fig. 2. Changes in volume of trapped gas (VTG) caused by drugs and exercise in per cent of predicted normal values. See text to Fig. 1.

RESULTS

The results are given in per cent of the predicted normal values for the children (Figs. 1 and 2) but also presented as the protective effect

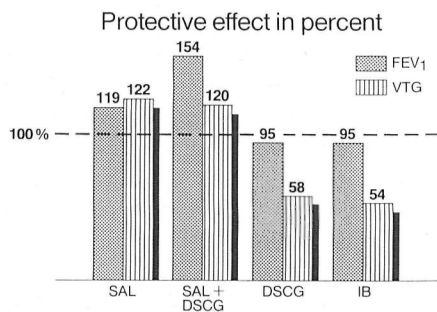


Fig. 3. Protective effect in per cent. 100 = complete protection against EIA as calculated by the equation: Protective effect = (change after placebo and exercise - change after drug and exercise) × 100/change after placebo and exercise.

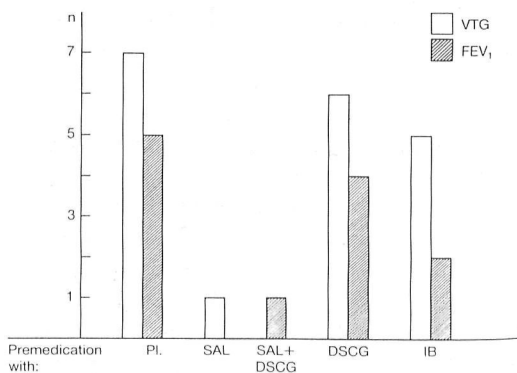


Fig. 4. Number of subjects showing significant EIA (change > 2 SD of the method) after premedication with placebo (PL), salbutamol (SAL), disodium cromoglycate (DSCG), and ipratropium bromide (IB).

in per cent. 100 % protection means no change between basal value and after exercise - according to the equation: Protective effect = (change after placebo - change after drug) × 100/change after placebo.

The results are presented in Figs. 1-4. The significance of differences between the different experimental situations are given in Table 2.

In the basal experiments the FEV₁ values in all tests were between 90 % and 95 % of predicted. No differences in FEV₁ or VTG were found between tests.

Effects of drugs. Salbutamol given after exercise in the placebo experiments increased FEV_1 to over the basal value but did not return the VTG value to the basal. All drugs, with the exception of DSCG, increased FEV_1 to almost 100 % of predicted, while VTG decreased after SAL and SAL + DSCG.

After DSCG, VTG showed a significant increase ($P < 0.01$). (Figs. 1 and 2).

Changes after exercise. In the placebo experiments a highly significant increase in VTG and decrease in FEV_1 were noted. After exercise in the experiments after drugs, FEV_1 was higher after SAL and DSCG + SAL than in the basal measurements and VTG was lower. After exercise a slight but significant decrease was seen in FEV_1 after premedication with DSCG and IB while VTG showed a highly significant increase (Figs. 1, 2).

The protective effect after SAL and SAL + DSCG was more than 100 % according to both FEV_1 and VTG. The protective effect of DSCG and IB was identical regarding FEV_1 (95 %) and similar regarding VTG (58 % and 54 %, respectively) (Fig. 3).

Significance of differences between the different experiments. Table 2 shows the significance of the change between the basal value and after exercise with placebo and the different drugs. The table shows the P -values for the differences between the experiments. Above the vertical line are the P -values for the changes in VTG

and below are those for FEV_1 . The values were thus significantly or highly significantly better after all drugs than after placebo. SAL and SAL + DSCG were significantly more effective in preventing EIA than DSCG and IB, but the combination was not significantly better than SAL alone. There was no significant difference between the efficacy of DSCG and IB for protecting against EIA.

Protective effect in the single subjects (Fig. 4). In our normal material (13) changes of up to ± 100 ml may occur in FEV_1 and up to 16 ml in VTG at rest. FEV_1 increased after exercise while VTG was unchanged. The subjects selected for the study had shown significant EIA according to VTG values after exercise. Consequently, all seven showed a highly significant increase in VTG in the control experiments. According to the decrease in FEV_1 , two had pronounced EIA with a decrease of about 1.5 l, one weak EIA and two not significant EIA. After SAL no one had significant EIA according to changes in FEV_1 , after DSCG + SAL one subject had significant EIA, after DSCG four subjects and after IB two. As measured by change in VTG, one subject had significant EIA after SAL, none after DSCG + SAL, six after DSCG and five after IB. Thus, by the number of subjects having measurable deterioration of function after exercise, SAL and SAL + DSCG gave almost complete protection, while IB was slightly more effective than DSCG. It can thus be deduced that EIA subjects had more pronounced bronchospasm after IB than after DSCG.

Table 2

P -values of the differences between the exercise-induced asthma provoked in the experiments. Abbreviation as used in the text. The differences in VTG values above the oblique line and those in FEV_1 below.

	VTG				
	Placebo	SAL	SAL + DSCG	DSCG	IB
Placebo		0.0005	0.001	0.005	0.05
SAL	0.01		NS	0.001	0.025
SAL + DSCG	0.005	NS		0.01	0.005
DSCG	0.025	0.01	0.025		NS
IB	0.025	0.05	0.025	NS	
	FEV_1				

DISCUSSION

Although several studies have examined the efficacy of single or combined drugs for the prevention of EIA, few have compared the effect of the commonly available dose aerosols. Some studies find β_2 -agonists to be superior (3, 7). However, recent official recommendations are contradictory about the drug of choice for the prevention of EIA (5, 8). Since the degree of EIA and the efficacy of drugs for its prevention vary between subjects, drug comparisons should be made in the same group of subjects. Metered aerosols must be preferred because of rapid action, easy handling and fewer side effects (9). We compared the preventive effect of metered aerosols with various pharmacological actions available in Sweden. There is no reason to believe that β_2 -agonists, if given in adequate doses, should differ in efficacy.

In the few earlier studies, comparing drugs with different pharmacological actions (3, 7), β_2 -agonists by inhalation were most effective for preventing EIA, while peroral theophylline, powder aerosol DSCG and atropine or IB as aerosols, were less effective and not significantly different. This study confirms the superior action of salbutamol.

Our patients were active in sports and interested in how drugs could diminish their EIA. As we knew from the literature that freons or other additives in metered aerosols can induce bronchospasm (18), we chose to use a peroral placebo, which cannot provoke EIA.

SAL, SAL + DSCG and IB gave the same degree of bronchodilation before exercise. However, only premedications containing SAL gave complete prevention of EIA. The primary effect of DSCG in this study was a significant bronchospasm as measured by VTG. This supports the complaints of irritation and increased bronchospasm when DSCG is taken without a bronchodilator. However, DSCG gave the same degree of protection as IB. The EIA after premedication with these drugs seemed mainly confined to small airways as indicated by the preferential increase in VTG. However, both EIA and bronchospasm provoked by the inhala-

tion of metacholine may give VTG increases of several 100 ml before any measurable decrease in FEV_1 occurs. Increased VTG is noted as slight tightness in the chest while decrease in FEV_1 as increased respiratory resistance. Whether decrease in FEV_1 is caused by involvement of the larger airways or large areas of the peripheral airways can not be judged by our methods or perhaps by any others. However, decrease in FEV_1 indicates a more pronounced EIA than increase in VTG. Thus, DSCG seems to be effective for the prevention of slight EIA, while less effective in subjects with pronounced disease, and the same probably applies to IB (16). The protection offered by DSCG is dose-dependent with a maximum protective factor of 85 % at 20 mg/ml (11). A dose-response protective effect was also found by Schoeffel et al. (12), who showed 2 mg from metered aerosol and 20 mg as dry powder by spinhaler to be equipotent. Thus 3 mg from metered aerosol should give optimal protection.

We found that the protective factor of IB was of the same magnitude as that of DSCG. Several authors have shown that the combination of a β_2 -agonist and IB by inhalation is superior to either drug alone (2, 10). The SAL + IB combination would certainly be worthwhile testing in subjects who were not protected with a β_2 -agonist alone. The vagal blocking provided by IB may be valuable in subjects with hyperirritability of the upper airways (10, 16). We measured the protection given by IB after 1 h when the effect is said to be maximum (10, 17), and repeated the same test protocol in two subjects 15 min after inhalation of the drug and obtained better protective effect. As the protective effect of IB may reach a maximum faster than the maximum bronchodilation, it should probably be used in close connection with exercise as with the other drugs.

The majority of asthmatic children are able to take part in physical exercise and play after premedication with a β_2 -agonist and, if necessary, the effect can be fortified by combining it with DSCG (17) or, possibly, IB (16). Some subjects, however, need continuous treatment with DSCG and/or inhaled steroids (14) in order to attain a level of physical fitness which

will reduce or eliminate their exercise-induced asthma (14).

REFERENCES

1. Arborelius, M., Svenonius, E. & Kautto, R.: Volume of trapped gas and maximum flow at 25% of vital capacity in exercise-induced asthma. In: *Small airways in health and disease*. Excerpta Medica 21-26, 1979.
2. Beck, R., Robertson, C., Galdés-Sebaldt, M. & Levi-son, H.: Clinical and laboratory observations. Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. *J. Pediatr.* 107, 605-608, 1985.
3. Bundgaard, A.: Exercise and the asthmatic. *Sports Med.* 2, 254-266, 1985.
4. Christensson, P., Arborelius, Jr M. & Kautto, R.: Volume of trapped gas in lungs of healthy humans. *J. Appl. Physiol.* 51, 172-175, 1981.
5. Engström, I.: Maintenance treatment in children with asthma. In: *Pharmacological treatment of bronchial asthma*. National Board of Health and Welfare Drug Information Committee, Sweden. 3, 146, 1986.
6. Godfrey, S.: Exercise-induced asthma. *Allergy* 33, 229-237, 1978.
7. Godfrey, S. & König, P.: Inhibition of exercise induced asthma by different pharmacological pathways. *Thorax* 31, 137-143, 1976.
8. Löwhagen, O. W.: Antiallergic agents. In: *Pharmacological treatment of bronchial asthma*. National Board of Health and Welfare Drug Information Committee, Sweden. 3, 21, 1986.
9. Newman, S. P.: Therapeutic aerosols. In Clarke, S. W. & Pavia, D. (eds.): *Aerosols and the lung*. Vol. 9, 197-224, Butterworths, London, 1984.
10. Pakes, G. E., Brodgren, R. N., Heel, R. C., Speight, T. M. & Avery, G. S.: Ipratropium bromide: a review of its pharmacological properties and therapeutic efficacy in asthma and chronic bronchitis. *Drugs* 20, 237, 1980.
11. Patel, K. R., Berkin, K. E. & Kerr, J. W.: Dose-response study of sodium cromoglycate in exercise-induced asthma. *Thorax* 37, 663-666, 1983.
12. Schoeffel, R. E., Andersson, S. D. & Lindsay, D. A.: Sodium cromoglycate as a pressurised aerosol (Vicrom) in exercise-induced asthma. *Aust. N.Z. J. Med.* 13, 157-161, 1983.
13. Svenonius, E. & Kautto, R.: The volume of trapped gas in healthy children aged 7-16. *Lung* 156, 71-77, 1979.
14. Svenonius, E., Kautto, R. & Arborelius, M.: Improvement after training of children with exercise-induced asthma. *Acta Paediatr. Scand.* 72, 23-30, 1983.
15. Svenonius, E., Lecerof, H., Lilja, B., Arborelius, Jr M. & Kautto, R.: The volume of trapped gas: a new and sensitive test for the detection of exercise-induced bronchospasm in children. *Acta Paediatr. Scand.* 67, 583-589, 1978.
16. Tashkin, D.: Use of anticholinergic drugs for asthma. *West. J. Med.* 144, 344-345, 1986.
17. Thomson, N. C., Patel, K. R. & Kerr, J. W.: Sodium cromoglycate and ipratropium bromide in exercise-induced asthma. *Thorax* 33, 694-699, 1978.
18. Yarbrough, J., Mansfield, E. & Ting, S.: Metered dose inhaler induced bronchospasm in asthma patients. *Ann. Allergy* 55, 25-27, 1985.

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