

A comparison of terbutaline inhaled by Turbuhaler[®] and by a chlorofluorocarbon (CFC) inhaler in children with exercise-induced asthma

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The present study compared the bronchodilating effect of inhalation from the Turbuhaler[®] (0.5 mg terbutaline $\times$ 2) with the effect of inhalation from the chlorofluorocarbon (CFC) inhaler (0.25 mg terbutaline $\times$ 4) in children aged 9–17 years with reproducible, exercise-induced asthma (EIA). The treatments were given on two occasions, 5 min apart (terbutaline 0.5 mg + 0.5 mg). The study was performed as a double-blind, double-dummy, and placebo-controlled trial in 12 asthmatic children. The study was conducted on three separate days. The bronchoconstriction was induced by steady running on a treadmill. Forced expiratory volume in 1 s ($FEV_{1.0}$), vital capacity (VC), and volume of trapped gas (VTG) were measured before and after the exercise test and after treatment. The study showed that the same amount of terbutaline inhaled from the Turbuhaler or from a CFC inhaler is equally effective for reversing EIA, and that the Turbuhaler is possibly more effective for treating spasm in small airways.

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Key words: CFC inhaler; children; exercise-induced asthma; $FEV_{1.0}$; Turbuhaler[®]; volume of trapped gas.

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Inhalation of β_2 -agonists is a well-established treatment of asthma, and its advantages include rapid onset of action, good efficacy, and few adverse effects. However, many patients are unable to use chlorofluorocarbon (CFC)-propelled inhalers efficiently despite adequate instruction. The most common error is failure to coordinate inhaler actuation with inspiration (4, 7, 12). These problems are likely to become worse during an acute attack of bronchospasm. In addition, CFC inhalers contain propellants and lubricants which may cause bronchoconstriction (16).

To overcome these problems, breath-actuated, dry-powder inhalers have been developed. The Turbuhaler[®] is a multidose, dry-powder inhaler containing pure terbutaline sulfate. A low inhalation air flow (≈ 30 l/min) through the Turbuhaler is enough to give maximal effect (10). A number of studies have shown that the Turbuhaler is effective and well accepted by patients in stable conditions and that inhalation of 0.5 mg terbutaline via the Turbuhaler is equipotent to 0.5 mg terbutaline inhaled via a CFC inhaler (9, 11). During acute bronchoconstriction,

higher doses than the dose used for prevention are normally used and recommended by physicians. Exercise-induced asthma (EIA) is suitable for testing the action of drugs in asthma, and it is reproducible and usually mild (1). $FEV_{1.0}$ is considered to measure changes in large airways. The volume of trapped gas (VTG) has been proposed as a more specific and sensitive test for detecting early bronchospasm during EIA than is $FEV_{1.0}$ (14).

The aim of this study was to compare the effect on lung function ($FEV_{1.0}$, VC, VTG) of inhalation from the Turbuhaler (0.5 mg terbutaline $\times$ 2) with that of inhalation from the CFC inhaler (0.25 mg terbutaline $\times$ 4) in acute bronchoconstriction provoked by exercise.

Material and methods

The study was of a double-blind, double-dummy, randomized, crossover design, and it was conducted on three separate study days. Twenty children were considered for inclusion. Twelve children (two girls) with well-known, exercise-induced asthma (EIA)

were included and completed the study. Inclusion criteria: age 7–17 years and a decrease in $FEV_{1.0} \geq 15\%$ after a 6-min exercise test. Exclusion criteria: hypersensitivity to sympathomimetics and cardiovascular, renal, or liver diseases. The mean age of the children was 13.8 years (9–17 years), mean height was 164 cm (138–185 cm), and mean weight was 58 kg (36–98 kg). The mean duration of their asthma was 12 years (8–15 years).

On the three study days, the children attended the clinic at the Department of Clinical Physiology, Malmö General Hospital, Sweden, and each child was tested at the same time of the day. Inhaled β_2 -agonists were withdrawn at least 6 h before the exercise test. If the patients used steroids, the doses of these were not changed. Other medications were not used by any child. Base-line $FEV_{1.0}$ (pre-exercise) was not allowed to vary by more than 15% between the study days. After a 6-min exercise, the patients needed to have a fall in $FEV_{1.0}$ of $\geq 15\%$ of base-line values. Moreover, the fall in $FEV_{1.0}$ could not vary by more than $\pm 5\%$.

Basal $FEV_{1.0}$ and VC were measured with a Bernstein type spirometer. VTG is the volume of nitrogen mobilized by maximal breaths after N_2 washout down to 2% expressed as air. VTG was measured as follows: with the patient breathing O_2 at tidal volume breaths, a nitrogen washout was continued until the end expiratory nitrogen reached 2% with an Ohio 700 nitrogen analyzer (Ohio, Houston, TX, USA). A stopcock was turned and the patients re-breathed with five maximum breaths into an empty, oxygen-washed rebreathing bag. VTG was defined (3) as:

$$VTG = \frac{TLC \times FN_2ER - FRC \times 0.02}{0.80}$$

TLC = total lung capacity

FN_2ER = N_2 fraction at end of rebreathing period
FRC = functional residual capacity

After base-line measurement of $FEV_{1.0}$, VC, and VTG, the exercise test was performed by a 6-min steady running on a treadmill with an inclination of 5°. The speed was adjusted to keep the heart rate at least 180 beats/min during the last 3 min.

Immediately after the exercise test, $FEV_{1.0}$, VC, and VTG were measured. After a decrease in $FEV_{1.0}$ of $\geq 15\%$, the first dose of study medication was given. Four min later, $FEV_{1.0}$ and VC were measured, and immediately afterwards (time 5 min) the second dose of study medication was given. After another 4 min (time 9 min), $FEV_{1.0}$ and VC measurements were repeated. Further measurements of $FEV_{1.0}$ and VC plus VTG were made after 14 and 15 min, respectively.

The study medication was given twice in a blinded, randomized order on the three different days and consisted of:

- 1) terbutaline (0.5 mg) by the Turbuhaler and placebo CFC inhaler
- 2) terbutaline (2×0.25 mg) by the CFC inhaler and placebo Turbuhaler
- 3) placebo Turbuhaler and placebo CFC inhaler.

The data were analyzed by a fixed-effects ANOVA with the factors patient and treatment. *P* values less than 0.05 were considered to be statistically significant.

Results

For two children, one of the three study days was considered to be invalid. One child did not get a fall of 15% after exercise, and another child had used inhaled β_2 -agonists less than 6 h before the clinic visit. These two days were excluded from analysis.

The mean pre-exercise base-line values in $FEV_{1.0}$

Table 1. Lung function values before exercise, after exercise, and after treatment (mean values, SD=standard deviation, *n*=number of patients)

	Turbuhaler			CFC inhaler			Placebo		
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD
$FEV_{1.0}$ (l)									
Base-line pre-exercise	11	3.16	1.06	11	3.19	1.11	12	3.12	1.14
0 min	11	2.33	0.96	11	2.34	0.94	12	2.26	0.97
4 min after	11	2.64	1.05	11	2.65	0.88	12	2.25	0.98
9 min after	11	2.67	1.04	11	2.91	0.91	12	2.38	1.02
14 min after	11	3.04	1.03	11	2.93	0.93	12	2.47	0.98
	Turbuhaler			CFC inhaler			Placebo		
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD
VTG (ml)									
Base-line pre-exercise	11	102	42	11	87	29	12	94	32
0 min	11	284	179	11	299	273	12	273	273
15 min after	11	119	72	11	174	159	12	180	118

were almost the same on the three study days (3.16, 3.19, and 3.12 l before the Turbuhaler, CFC inhaler, and placebo, respectively; Table 1). After exercise, there was a mean decrease in FEV_{1.0} of about 0.8 l to 2.33, 2.34, and 2.26 l. The percentage fall was within 5% in all children on the three study days (Table 2). Already 4 min after the first inhalation, there was an increase after active treatment to 2.64 l with the Turbuhaler and to 2.65 l with the CFC inhaler. After placebo inhalation, there was a decrease of 0.01 l. There was a statistically significant difference between active and placebo treatments ($P = 0.03$). Fourteen min after the start of first inhalation, the mean values of FEV_{1.0} had increased further after active treatments to 3.04 and 2.93 l with the Turbuhaler and the CFC inhaler, respectively. After placebo inhalation, the increase was 0.21 l to 2.47 l. A statistically significant difference was shown between the active and placebo treatments ($P = 0.007$). No statistically significant differences between the two active treatments were seen at either 4 or 14 min after the start of inhalation. Table 3 shows the individual percent increases in FEV_{1.0}.

The change in VC showed a pattern similar to that of FEV_{1.0}. The mean base-line values were 4.20, 4.11, and 4.06 l before the Turbuhaler, the CFC inhaler, and placebo treatments.

The mean pre-exercise base-line values of VTG were 102, 87, and 94 ml before the Turbuhaler, the CFC inhaler, and placebo, respectively. After the exercise test, there were increases to 284, 299, and 273 ml, respectively. Fifteen min after start of inhalation of active treatment, the mean values of VTG were 119 and 174 ml after the Turbuhaler and the CFC inhaler, respectively. After placebo treatment, the mean VTG decreased to 180 ml (Table 1). The statistical analysis showed a significant difference among all three treatments ($P = 0.02$). Pairwise comparison showed a statistically significant difference only between the terbutaline Turbuhaler and placebo ($P = 0.005$). However, there was neither any statis-

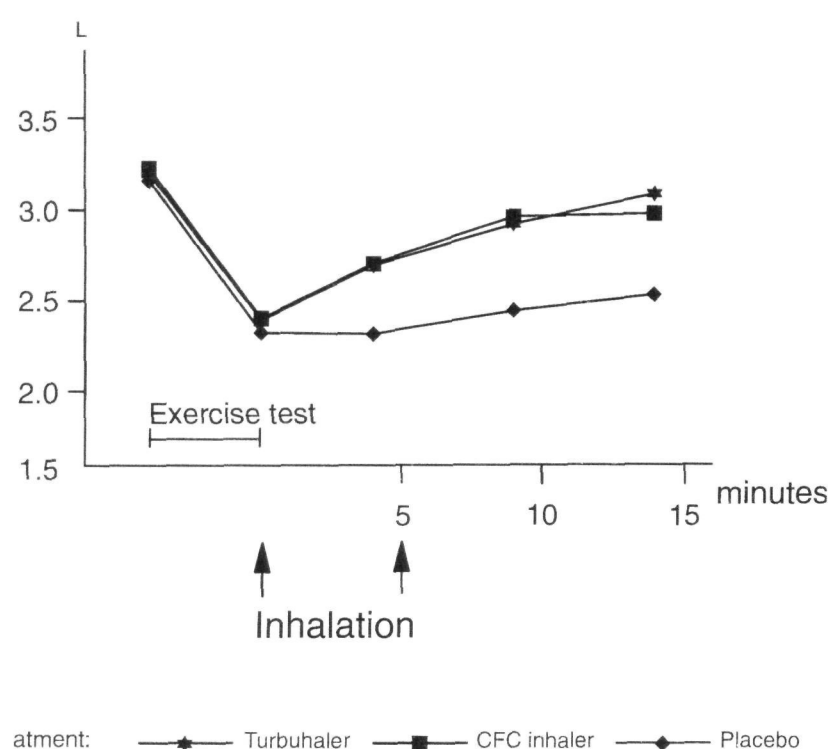


Fig. 1. FEV_{1.0} (mean values).

Table 3. FEV_{1.0} (%) individual values (increases from base line to 15 min after start of inhalation). Base line is point where at least 15% fall was achieved

Patient No.	Turbuhaler	CFC inhaler	Placebo
1	33	65	23
3	—	47	11
7	12	13	-5
10	35	—	11
13	5	3	7
14	50	40	14
15	178	126	92
16	16	36	-29
17	16	15	10
18	58	-8	12
19	28	12	7
20	24	26	16

tically significant difference between the terbutaline CFC inhaler and placebo nor between the terbutaline Turbuhaler and terbutaline CFC inhaler. Table 4 shows the individual percent decreases in VTG.

Discussion

Exercise-induced asthma (EIA) should preferably be prevented by inhalation of a β -agonist before exercise (6). If patients develop EIA in spite of that pretreatment, the basic asthma needs more intense treatment with anti-inflammatory drugs such as topical corticosteroids or disodium cromoglycate. Moreover, the combination of a β -agonist and disodium cromoglycate inhaled immediately before exercise has been shown to offer better protection than either drug alone (5, 13, 15). However, if EIA occurs in spite of premedication, a higher dose of β -agonists

Table 2. Percent fall after exercise (individual values)

Patient No.	Turbuhaler	CFC inhaler	Placebo
1	26	32	35
3	—	22	22
7	18	32	18
10	24	—	20
13	21	18	29
14	32	23	25
15	52	52	62
16	46	38	37
17	15	19	17
18	40	43	46
19	18	77	15
20	15	20	18

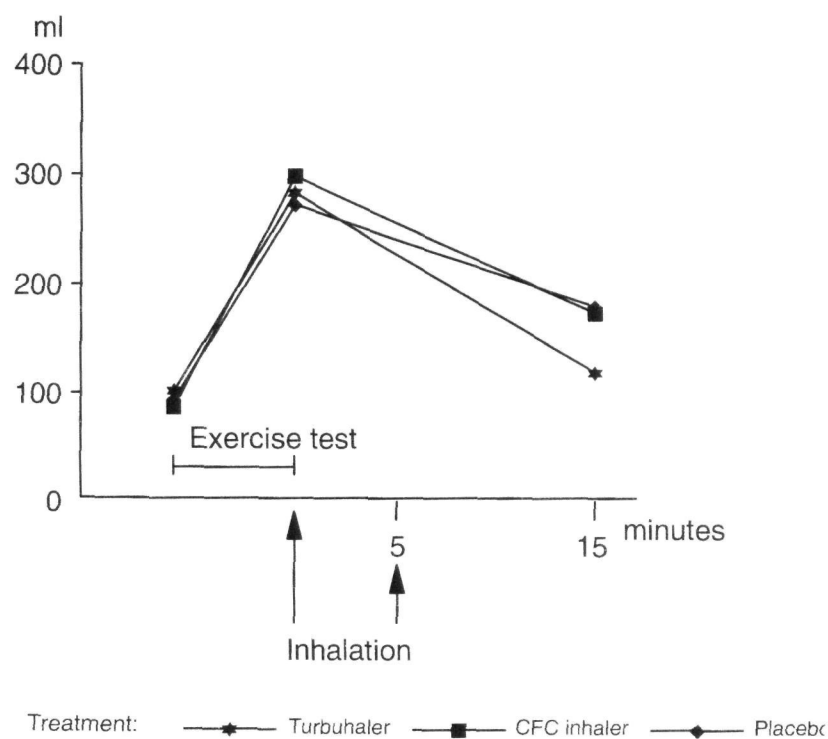


Fig. 2. VTG (mean values).

Table 4. VTG (%) individual values (decreases from base line to 15 min after start of inhalation. Base line is point where at least 15% fall was achieved)

Patient No.	Turbuhaler	CFC inhaler	Placebo
1	74	66	54
3	-	65	17
7	27	28	14
10	56	-	47
13	54	-5	33
14	29	-13	-6
15	77	74	25
16	17	14	-14
17	37	17	-13
18	81	40	59
19	72	31	-70
20	54	57	41

from a CFC inhaler commonly ends the attack within minutes. Some patients have claimed that the Turbuhaler is inferior to their previously used CFC inhaler for rapid relief of EIA. Even if there is ample proof in the literature (8) that dry-powder inhalers and CFC inhalers are equally effective for prevention of EIA, it may be possible that dry-powder inhalers during acute EIA penetrate constricted peripheral airways less effectively than CFC inhalers, at least in some patients.

Measurements of VTG were included. They presumably quantify obstruction in small airways (2). Lack of effect of the drug treatment, defined as less improvement after active drug than with placebo, was noticed after both the Turbuhaler and CFC treatment. As shown in Tables 1 and 2, the variability is great both between the patients and between the study drugs. However, the mean value of VTG

after CFC inhaler was identical to the mean value after placebo 15 min after inhalation, while it was more than 50 ml lower after Turbuhaler inhalation and close to base-line values.

It appears that the effect on large airways measured as $FEV_{1.0}$ was the same after the Turbuhaler as after the CFC inhaler, but a small difference would be noticed when small airways function is measured by VTG. Still, both drugs seemed to have little effect in a few patients, a finding which stresses the fact that EIA should be prevented rather than cured. However, the results indicate that terbutaline inhaled from the Turbuhaler perhaps penetrates better to small airways than if inhaled from the CFC inhaler. Thus, our conclusion is that the same amount of terbutaline inhaled from the Turbuhaler or from a CFC inhaler is equally effective for aborting EIA and the Turbuhaler is possibly more effective for treating spasm in small airways.

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