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A new multiple dose powder inhaler, (Turbuhaler®), compared with a pressurized inhaler in a study of terbutaline in asthmatics

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A new multiple dose powder inhaler, (Turbuhaler®), compared with a pressurized inhaler in a study of terbutaline in asthmatics. G. Persson, E. Gruvstad, E. Ståhl.

ABSTRACT: Twelve adult asthmatic patients participated in an open, randomized, cross-over comparison between cumulatively increasing doses of terbutaline sulphate administered via the multiple dose powder inhaler (Turbuhaler) or via a pressurized inhaler. Turbuhaler and the pressurized inhaler showed equipotency both with respect to bronchodilatation and side effects. Both treatments produced a significant increase in pulmonary function measurements, forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). No increase in pulse rate was seen with either treatment but there was an increase in tremor at higher doses with both treatments. Inhalation of ß-agonists via Turbuhaler seems to be an effective way of treating asthma.

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Inhalation of ß-agonists is well established in the treatment of asthma and has advantages such as rapid onset of action, good efficacy at a low dose and few side-effects. However, many patients are unable to use a pressurized inhaler efficiently despite adequate tuition. The most common error is failure to coordinate inhaler actuation with inspiration [1–3]. In addition, pressurized inhalers contain propellants and lubricants which may cause bronchoconstriction [4] or have potential arrythmogenic effects [5].

To overcome this problem breath-actuated dry powder inhalers have been developed. The new powder inhaler, used in the present study, Turbuhaler®, differs from the bronchodilator inhalers currently available in two major respects. Firstly, Turbuhaler is a multiple dose powder inhaler, *i.e.* each Turbuhaler contains two hundred doses ready to inhale. Secondly, Turbuhaler dispenses pure terbutaline sulphate. Carrier substances such as lactose or glucose are not required. The absence of a carrier substance in Turbuhaler reduces the risk of provoking bronchial irritation.

The technical construction of Turbuhaler has been described by WETTERLIN [6]. Turbuhaler is ready for instant use; a metered-dose is prepared by twisting the turning grip at the bottom of the inhaler (fig. 1). The drug flows from a reservoir down onto a dosing disc. Fine holes on the dosing disc are filled up and a metered-dose is made available in the inhalation channel as the rotating disc moves round. When the patient inhales, the micronized drug is carried into the airways in the inhaled air.

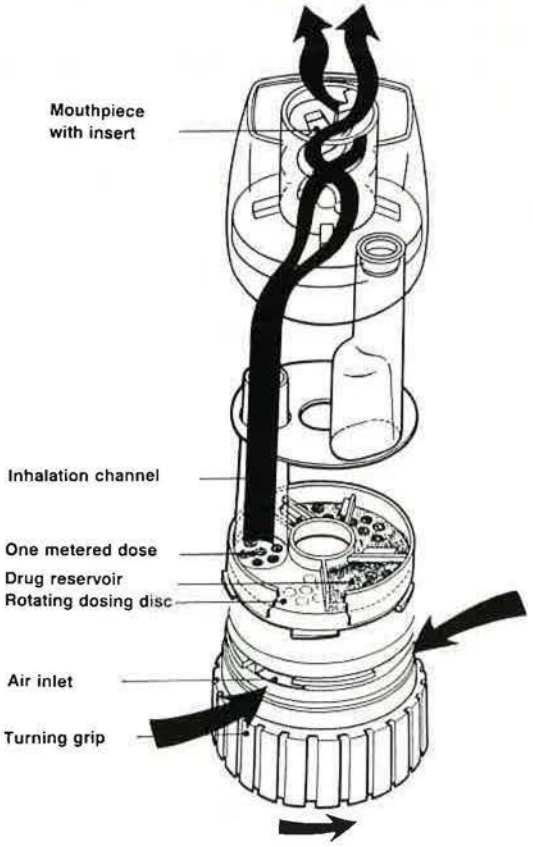

Fig. 1 – Technical description of Turbuhaler®.

Early investigations on salbutamol dry powder inhalers showed greater forced expiratory volume in one second (FEV_1) increase in asthmatic patients treated with pressurized inhalers than with dry powder inhalers [7, 8]. It has recently been shown in a number of studies, however, that bronchodilators in powder form are as effective as aerosols of the same substances *e.g.* salbutamol [9, 10] and fenoterol [11–14]. The aim of the present study was to compare the bronchodilator response of terbutaline sulphate when administered via the new powder inhaler (Turbuhaler) and via a pressurized inhaler.

Patients and Methods

Thirteen patients with mean age 39 yrs (range 20–59 yrs) (six males and seven females) with chronic, stable asthma entered the study. Clinical data are given in table 1. Within a fourteen-day period prior to the study, all patients had shown at least a 20% increase in FEV_1 and an absolute FEV_1 >70% of predicted normal value, after inhalation of two puffs of 0.25 mg terbutaline sulphate via a pressurized aerosol.

Before each study day, theophylline, oral inhaled or $ß_2$-receptor-stimulants and anticholinergics were withdrawn from all thirteen patients within the previous 48, 12/8 and 48 h, respectively. Basal FEV_1 was not allowed to vary more than 15% between the two days of the study. One patient was excluded from the analysis for that reason.

The patients were informed verbally and in writing of the nature and purpose of the study and their written consent was obtained.

The study was approved by the Ethical Committee of the University of Lund and the National Board of Health and Welfare.

Study Design

The study was an open, randomized, cross-over comparision between cumulatively increasing doses of terbutaline sulphate administered via the powder inhaler (Turbuhaler®) or via the pressurized inhaler.

The patients attended the clinic three times. On the first day, the reversibility was tested and then on two days, at least a week apart, they used either the pressurized inhaler or the powder inhaler. The patients were not allowed to drink coffee, tea or chocolate in the morning before and during the study.

The patients arrived at 7 am and after a resting period of one hour, the basal values of FEV_1, forced vital capacity (FVC) and pulse rate were measured. Tremor was measured at 1 h and immediately before the administration of terbutaline and the mean of these values was used as the basal value.

Terbutaline sulphate (0.25 mg, 0.25 mg, 0.5 mg, 2x0.5 mg and 4x0.5 mg) was given as cumulative doses with 30 min intervals. After the highest dose, 4x0.25 mg terbutaline sulphate were given via a pressurized inhaler to test whether maximal response had been reached.

The following measurements were performed:

1) FEV_1 and FVC were recorded with a Vitalograph, and the highest value of two attempts was registered;

2) pulse rate was measured by palpation of the radial artery;

3) skeletal muscle tremor was measured by an optoelectronic tremorgraph (Draco, Lund, Sweden). The right arm was supported from the elbow and the right hand was supported except for the middle finger. Middle finger tremor was registered by an optoelectronic displacement transducer which measured the distance to a reflecting tape attached to the right middle finger. The displacement signal was transformed to express the total distance moved by the finger over a ten-second period. FEV_1,

Table 1. – Clinical details of patients and basal lung function values

Patient No.	Previous drug treatment	Basal FEV_1		Reversibility on test day FEV_1 Increase after 2x0.25 mg terbutaline
		l	% pred	% basal value
1	IB, OB, IS	2.55	69	31
2	IB, OB, IS	1.75	63	23
3	IB	3.10	61	37
4*	IB, TH			
5	IB, OB, TH	3.60	82	25
6	IB, TH	2.70	63	28
7	IB, OB, IS, TH	2.15	48	49
8	IB	2.00	56	35
9	IB, OB, IS	2.85	66	22
10	IB, OB, IS	1.45	58	28
11	IB, OB, IS	3.90	83	21
12	IB, OB, IS, TH	1.75	80	20
13	IB, OB, IS, TH	1.20	38	95

* Excluded because basal FEV_1 value on the two days varied more than 15%. IB: inhaled ß-stimulant; OB: oral ß-stimulant; IS: inhaled corticosteroid; OS: oral corticosteroid; TH: theophylline.

FVC and pulse rate were registered 20 min after each dose and tremor 25 min after each dose.

In order to obtain optimal efficacy each patient was instructed to inhale slowly and deeply through the pressurized inhaler and to actuate the dose at the beginning of inhalation. When using the powder inhaler, the patients were asked to inhale deeply since the resistance of the inhaler forced the patients to inhale slowly.

In order to ensure that the inhalations were correctly performed, the flow-volume curve at each inhalation was registered. The pressurized inhaler and the powder inhaler were attached to a hot wire spirometer (model 403, Monaghan), an oscilloscope and a Kipp & Zonen x/y-recorder according to a technique described by MORÉN *et al.* [15]. Thus, the patients and the technicians could follow the inspiratory flow curve on the oscilloscope. Peak inspiratory flow rate (PIFR) and forced inspiratory volume (FIVC) were registered by the spirometer.

Cumulative dose-response curves were constructed for mean increase over basal values for FEV_1, FVC and tremor. The results were analysed statistically using analysis of variance for the area under the curve (AUC) and Student's paired t-test for individual doses.

Results

The mean peak inspiratory flow rate (PIFR)±SEM through the powder inhaler was 57±1 $l \cdot min^{-1}$ and the mean inhaled volume 3.3±0.1 l. The mean peak inspiratory flow rate through the pressurized inhaler was 170±4 $l \cdot min^{-1}$ and the mean inspired volume 3.9±0.1 l.

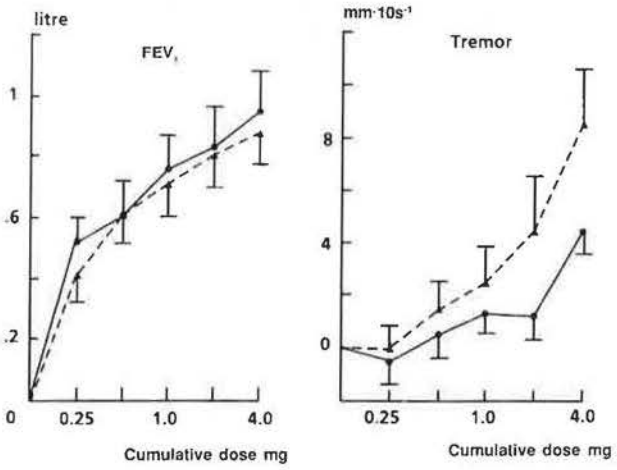

Fig. 2. – Increase in FEV_1, FVC and tremor over basal value after inhalation of terbutaline sulphate via Turbuhaler (●—●) or via pressurized inhaler (▲—▲). Mean±SEM.

Mean basal FEV_1±SEM values were 2.6±0.2 l and 2.7±0.2 l on Turbuhaler and pressurized inhaler treatment days, respectively. Both treatments resulted in a significant increase over basal value even after the first dose ($p<0.001$) (fig 2), without a statistically significant difference between the two treatments either regarding AUC or individual doses. The increase in FEV_1 after four extra puffs of terbutaline sulphate was not statistically significant, showing that maximal response had already been reached with both devices.

Mean basal FVC±SEM values were 3.9±0.4 l and 4.1±0.4 l on Turbuhaler and pressurized inhaler treatment days, respectively. Again, there was a significant increase ($p<0.01$) over the basal value from the first dose but no statistically significant difference in FVC between the two devices throughout the study either regarding AUC or individual doses.

Mean basal tremor ± SEM was 10±1 $mm \cdot 10s^{-1}$ and 12±2 $mm \cdot 10s^{-1}$ on Turbuhaler and pressurized inhaler treatment days, respectively. The tremor dose-response curves are shown in figure 2. After the last dose (cumulative dose 4 mg) there was a significant increase in tremor with both devices ($p<0.01$). No significant difference was found between the two devices, either regarding AUC or individual doses. The absolute increase in tremor was higher for the pressurized inhaler but this could be attributed mostly to one patient.

No increase in pulse rate occurred with either treatment.

Discussion

Up to 60% of the patients regularly using pressurized inhalers have faulty inhaler technique [16–18] thus severely impairing the effect of the bronchodilator drug [17, 18]. For these patients, treatment with powder inhalers would be a more reliable alternative.

This comparison between the powder inhaler and the pressurized inhaler was carried out in asthmatics who did not show any adverse reactions to the additives in the pressurized aerosol. The patients were under strict observation to check that they used their inhalers correctly. The results of the study showed an equipotency between terbutaline sulphate powder inhaler and pressurized inhaler and also a dose-dependent increase in FEV_1, FVC and tremor. A normal single dose does not exceed 1 mg terbutaline and no statistically significant increase in tremor was seen either with Turbuhaler or pressurized inhaler until the last dose (cumulative dose 4 mg).

The mean peak inhalation flow rate was lower through Turbuhaler than through the pressurized inhaler, due to the higher resistance to inhalation through Turbuhaler. PEDERSEN and co-workers [19, 20] have shown that children should inhale as fast as possible through other types of powder inhalers (Rotahaler and fenoterol powder inhaler) to obtain maximum benefit from the treatment. In this study, the lowest inhalation flow rate at the first dose was 33 $l \cdot min^{-1}$. The resulting increase in FEV_1 for this patient after inhalation of 0.25 mg terbutaline sulphate with this slow flow rate was very good (almost 1 l), 23% increase over basal value. This indicates that Turbuhaler is effective even at low flow rates, and that patients will benefit from this treatment even during acute attacks.

In conclusion, this study showed equipotent bronchodilatory efficacy from terbutaline when administered via Turbuhaler and via a pressurized inhaler. Additional

advantages of Turbuhaler, such as absence of coordination problems and additives, make it an attractive alternative in the daily treatment of asthma.

References

1. Crompton GK. – Problems patients have using pressurized aerosol inhalers. *Eur J Respir Dis*, 1982, 63 (Suppl. 119), 101–104.
2. Epstein SW, Manning CPR, Ashley MJ, Corey PN. – Survey of the clinical use of pressurized aerosol inhalers. *Can Med Assoc J*, 1979, 120, 813–816.
3. Shim Ch, Williams MH. – The adequacy of inhalation of aerosol from canister nebulizers. *Am J Med*, 1980, 69, 891–894.
4. Yarbrough J, Mansfield LE, Ting S. – Metered dose inhaler induced bronchospasm in asthmatic patients. *Ann Allergy*, 1985, 55, 25–27.
5. Thiessen B, Pedersen OF. – Effect of freon inhalation of maximal expiratory flows and heart rhythm after treatment with salbutamol and ipratropium bromide. *Eur J Respir Dis*, 1980, 61, 156–161.
6. Wetterlin K. – Turbuhaler^{R} - a new powder inhaler for administration of drug to the airways. *Pharmaceutical Research*, 1988, 5, 506–508.
7. Duncan D *et al.* – Comparison of the bronchodilator effects of sabutamol inhaled as a dry powder and by conventional pressurized aerosol. *Br J Clin Pharmacol*, 1977, 4, 669–671.
8. Hetzel MR, Clark TJH. – Comparison of salbutamol Rotahaler with conventional pressurized aerosol. *Clin Allergy*, 1977, 7, 563–568.
9. Latimer KM *et al.* – Salbutamol: comparison of bronchodilating effect of inhaled powder and aerosol in asthmatic subjects. *Can Med Assoc J*, 1982, 127, 857–859.
10. Svedmyr N *et al.* – The effect of powder aerosol compared to pressurized aerosol. *Eur J Respir Dis*, 1982, 63 (Suppl. 119), 81–88.
11. Boye, Kornstad. – A comparison of fenoterol powder capsules and fenoterol metered dose spray in bronchial asthma. *Eur J Respir Dis*, 1983, 64, (Suppl 130), 9–11.
12. Chambers S et al. – Inhaled powder compared with aerosol administration of fenoterol in asthmatic children. *Arch Dis Child*, 1980, 55, 73–74.
13. Dirksen H, Groth S. – Fenoterol inhalation powder as an alternative to treatment with the metered dose inhaler. *Eur J Respir Dis*, 1983, 64 (Suppl. 130), 48–53.
14. Salorinne Y, Siren R. – Ventilation effects of fenoterol powder and freon-propelled aerosol in patients with asthma. *Eur J Respir Dis*, 1983, 64 (Suppl. 130), 6–8.
15. Morén F *et al.* – Mode of inhalation for trained and untrained asthmatics using a pressurized aerosol. *Respiration*, 1984, 45, 56–60.
16. Simonsson BG. – The use of bronchodilating dose-aerosol. *Läkartidningen*, 1976, 73, 1407–1409.
17. Lahdensuo A, Muittari. – Bronchodilator effects of a fenoterol metered dose inhaler and fenoterol powder in asthmatics with poor inhaler technique. *Eur J Respir Dis*, 1986, 68, 332–335.
18. Lindgren S, Bake B, Larsson S. – Clinical consequences of inadequate inhalation technique in asthma therapy. *Eur J Respir Dis*, 1987, 70, 93–98.
19. Pedersen S. – How to use a rotahaler. *Arch Dis Child*, 1986, 61, 11–14.
20. Pedersen S, Steffensen G. – Fenoterol powder inhaler technique in children: influence of inspiratory flow rate and breath-holding. *Eur J Respir Dis*, 1986, 68, 207–214.

RÉSUMÉ: Douze adultes asthmatiques ont participé à une comparaison ouverte mais avec randomisation en permutation croisée entre des doses croissantes et cumulatives de sulfate de terbutaline, administrées par un inhalateur de poudre à doses multiples (le turbuhaler) ou via un aérosol doseur. Le turbuhaler et l'aérosol doseur ont montré une équipotence en ce qui concerne la broncho-dilatation et les effets secondaires. Les deux traitements ont entraîné une augmentation significative des mesures fonctionnelles pulmonaires: VEMS et capacité vitale forcée. L'on n'a observé aucune augmentation du pouls dans aucun des deux traitements, mais il y avait une augmentation des tremblements aux fortes doses dans les deux cas. L'inhalation de bêta-agonistes par le turbuhaler semble donc une maniére efficace de traiter l'asthme.