

Terbutaline as powder inhalation from Bricanyl Turbuhaler compared to terbutaline as nebulizer solution in severe chronic airways obstruction

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ABSTRACT: Twenty two adults with severe chronic airways obstruction- FEV_1 from 14 to 57% of predicted - participated on two consecutive days in an open cross over comparison of inhalation of 2 mg terbutaline powder by Bricanyl Turbuhaler and 5 mg terbutaline by a conventional jet nebulizer (Pari Inhalierboy). All participants were domiciliary users of nebulized terbutaline previous to inclusion in this study. The mean (SD) maximal increase in FEV_1 within the 60 minutes following inhalation by Turbuhaler and by Pari Inhalierboy was 27% (15%) and 28% (15%). The mean (SD) maximal increase in FVC was 30% (20%) and 29% (16%). The differences were not statistically significant. All participants were able to produce inspiratory flows high enough to use the Turbuhaler. The study suggests that it will be possible to replace the use of nebulizers with powder inhalations, as far as the bronchodilating effects are concerned.

Eur Respir J., 1989, 2, 716-720

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Keywords: Chronic airways obstruction; inspiratory flow; nebulizer; powder inhalation; terbutaline.

Received October 1988

About 3400 Danish adults had a nebulizer for domiciliary use in November 1987 - equivalent to a prevalence of 1 per 1000 of the adult population (result of an unpublished enquiry among Danish hospital departments). The majority of the patients who use a nebulizer at home, suffer from severe chronic airways obstruction. The nebulizer treatment is predominantly prescribed when other types of inhalation therapy are ineffective. The poor effect of the metered dose inhalator (MDI) is often caused by lack of coordination between inhalation and dose release [1], and an increase in the number of prescribed doses does not solve this particular problem. The addition of the different shapes of spacers to the MDI appears to relieve the problem. Another approach to the coordination problem is the principle of powder inhalation, where the energy needed to create the aerosol does not originate from the release of a pressurized gas, but from the inspiratory effort of the patient. The use of powder inhalators has been limited by the inconvenience of loading the device before each dose, and the inability of some patients to inhale with enough force to empty the device [2, 3]. The Bricanyl Turbuhaler from Astra/Draco is a new multidose powder inhalator with a high internal resistance, which produces a relatively slow flow of particles into the airways, but at the same time a high velocity through the inhaler. This design allows generation of respirable particles even at a low inspiratory flow [4].

The aim of the present study was to compare the

bronchodilating effect of the usually prescribed dose of 5 mg terbutaline by Pari Inhalierboy to 2 mg terbutaline from Bricanyl Turbuhaler. The study was the first in a series of clinical investigations initiated in order to answer the question: can dry powder inhalers replace the domiciliary nebulizer treatment in patients with severe chronic obstruction of the airways? The present dose of 2 mg from the Turbuhaler was prior to the study estimated to be equipotent to 5 mg terbutaline by Pari Inhalierboy. Patients with the most severe bronchial obstruction were studied in order to be able to identify possible patients who might be unable to use the device because of impaired lung function.

Replacement of the nebulizer with high dose beta-stimulant therapy by a multidose powder inhalator could be of major importance to the patients. The Bricanyl Turbuhaler is easy to use and easy to carry along in contrast to the most common types of jet-nebulizers, which are driven by stationary air pumps, thus restricting the mobility of the patient. There is no known risk of a bacterial contamination of the airways from a powder inhalator, and the necessary drug doses are presumably smaller than the very high doses recommended for use by nebulizers [5].

Patients

Twenty five adult outpatients were consecutively included in the study. The selection criteria were:

domiciliary treatment with a nebulizer for at least 4 months, chronic obstructive lung disease according to the American Thoracic Society criteria [6], forced expiratory volume in one second (FEV_1) less than 50% of predicted (reference values as recommended by the Danish Thoracic Society) at the last preceding visit and ability to cooperate in the study. All of the patients completed the study. A difference between baseline FEV_1 on the 2 study days of more than 20% (of the average for the two days) was considered unacceptable, and data from 3 patients were excluded for this reason. Data from the remaining 22 participants (10 women and 12 men) were used in the evaluation. The mean (SD) age was 69.5 (9.5) years. The baseline lung function is shown in table 1. All participants had a history of smoking, 7 were actual smokers. The median time since the start of nebulizer treatment was 1 year 9 months (range 5 months to 8 years 6 months), and the dosage was 5 mg terbutaline 1 to 3 times a day. The majority of the participants used an oral beta agonist as well as a beta agonist by MDI, oral xanthines and steroids by MDI and/or as tablets in addition to the inhalations by a nebulizer.

All patients received verbal and written information before giving their consent to participate. The study was in accordance with the Helsinki Declaration II, and was approved by the local Ethical Committee.

Table 1. - Mean (SD) baseline FEV_1 and FVC on day 1 and day 2 (n = 22)

	Day 1	Day 2
FEV_1 (l)	0.68 (0.22)	0.65 (0.17)
FEV_1 (% pred.)	27.4 (8.9)	26.5 (7.0)
FVC (l)	1.66 (0.34)	1.67 (0.49)
FVC (% pred.)	49.1 (8.2)	49.3 (12.7)

FEV_1 : forced expiratory volume in one second; FVC: forced vital capacity

Methods

The study was carried out at the patients, home. The two types of treatment were given according to a randomized, open cross-over design, at the same time in the morning on two consecutive days. The patients were not permitted to use oral bronchodilators or inhalation by the nebulizer from the previous evening. Bronchodilators by metered dose inhalator were discontinued for at least 4 hours.

Each participant inhaled 2 ml nebulizer solution containing 5 mg terbutaline sulphate from a jet nebulizer (Pari Inhalierboy) or 2 mg terbutaline sulphate as powder (4 doses) from a Bricanyl Turbuhaler. All patients used the same Pari Inhalierboy, and used it until the nebulizer chamber was empty (most patients do this in 5 to 10 minutes). A pause of 2 minutes was interposed between each inhalation by the Turbuhaler in order to match this.

On both days the FEV_1 and the forced vital capacity (FVC) were measured by a portable pneumotachograph (Vitalograph Compact) before inhalation and at 5, 15, 30, 45 and 60 minutes after. Three forced expirations were carried out before inhalation. One or two attempts were accepted in some cases after inhalation, if the patient was too breathless to complete three forced expirations. The highest FEV_1 and FVC at each time were chosen.

In order to measure the peak inspiratory flow (PIF) and the forced inspired volume (FIV) during inhalation the Turbuhaler was mounted inside an adapter and serially connected to the Fleisch tube with only the mouthpiece protruding. The adapter was disconnected between each inhalation in order to load the next dose by twisting the bottom piece of the Turbuhaler.

The heart rate was recorded before and 5 minutes after inhalations from both the Pari Inhalierboy and the Turbuhaler.

The risk of type 1 statistical error was chosen to 5% (double sided), the power was chosen to 95%, and the sample size was calculated accordingly. The data analysis showed that the actual power of the study was about 95%. There were no significant signs of a carry-over or periodic effect when the data was tested as suggested by HILL and ARMITAGE [7], so paired statistical analysis were applied. The possibility of a Gaussian distribution of the studied variables could not be excluded by means of the Kolmogorov - Smirnov Goodness of Fit Test and therefore parametric tests were used for the data analysis.

Results

The baseline FEV_1 and FVC and the maximal values within 60 minutes after the inhalations are listed in table 2. The mean absolute increase in FEV_1 and in FVC were small, but statistically significant, at all times after both types of inhalation ($p < 0.002$, paired t-test).

Figures 1 and 2 show the increase in FEV_1 and FVC over the baseline after the inhalations. The mean (SD) maximal increase in FEV_1 after inhalation by Turbuhaler and by Pari Inhalierboy was 27% (15%) and 28% (15%), respectively. The mean (SD) maximal in-

Table 2. - Baseline FEV_1 and FVC and the maximal values within 60 minutes after the 2 types of inhalation (tested at 5, 15, 30, 45 and 60 minutes after the inhalation).

	FEV_1 (l)				FVC (l)			
	Pari Inhalierboy		Turbuhaler		Pari Inhalierboy		Turbuhaler	
	Baseline	Max	Baseline	Max	Baseline	Max	Baseline	Max
Mean	0.66	0.84	0.67	0.85	1.68	2.16	1.66	2.14
SD	0.17	0.22	0.22	0.26	0.39	0.53	0.46	0.58

Symbols: see table 1.

crease in FVC was 30% (20%) and 29% (16%). The differences were not statistically significant (paired t-test). In absolute terms the mean maximal increases in FEV₁ after inhalation were 182 ml (Pari Inhalierboy) and 174 ml (Turbuhaler). The 95% confidence limits of the difference between maximal FEV₁ increase (Pari Inhalierboy minus Turbuhaler) were -21 ml to +37 ml. The mean maximal increases in FVC after inhalation were 485 ml (Pari Inhalierboy) and 476 ml (Turbuhaler). The 95% confidence limits of the difference between maximal FVC increase (Pari Inhalierboy minus Turbuhaler) were -102 ml to +118 ml.

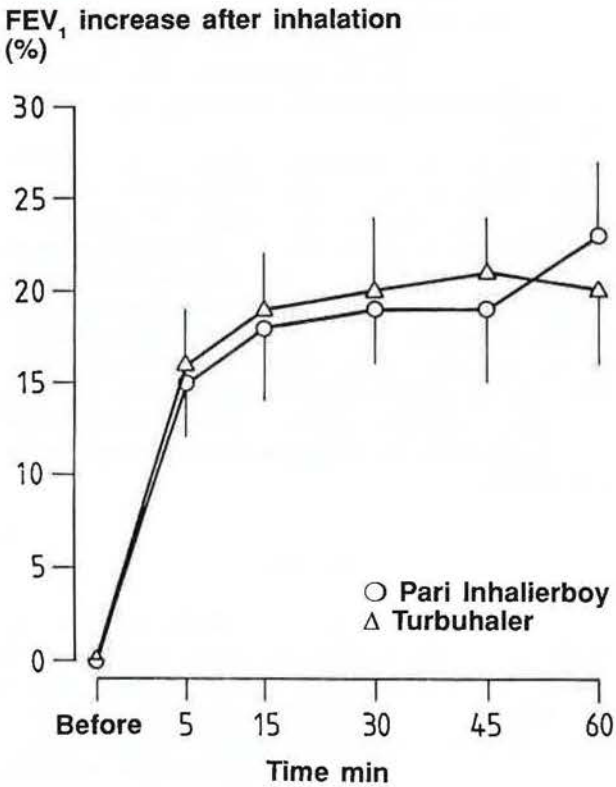


Fig. 1. - FEV₁ increase (% of baseline) after inhalation of 5 mg terbutaline from a jet nebulizer (Pari Inhalierboy) and 2 mg terbutaline powder from Bricanyl Turbuhaler. Mean \pm SEM, n=22.

FVC increase after inhalation (%)

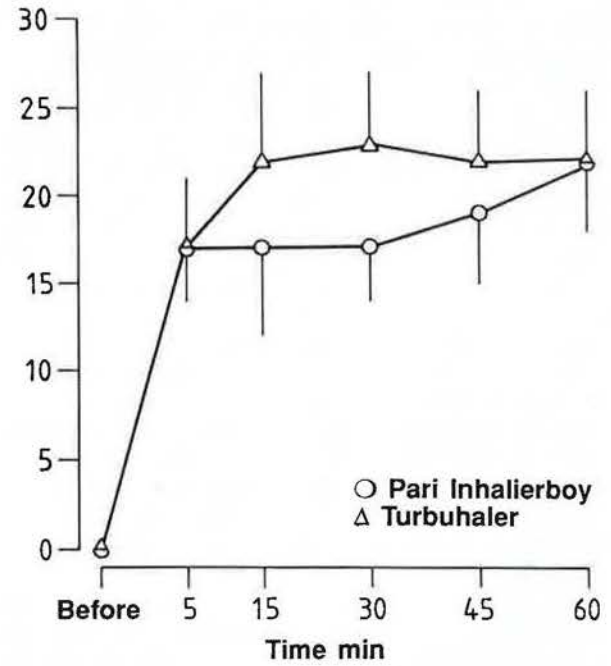


Fig. 2. - FVC increase (% of baseline) after inhalation of 5 mg terbutaline from a jet nebulizer (Pari Inhalierboy) and 2 mg terbutaline powder from Bricanyl Turbuhaler. Mean \pm SEM, n=22.

Thirteen of the 22 participants indicated that the effect of the inhalation was the same for the two types of treatment. Three preferred inhalation by the Pari Inhalierboy, and 6 preferred inhalation by the Turbuhaler.

Table 3 describes the PIV and FIV for the 4 inhalations through the Turbuhaler and the calculated average for each participant. The average PIV or FIV for each participant were not significantly correlated to the maximal increase in FEV₁ or FVC (as % of baseline) after inhalation by Turbuhaler (standardized for individual "bronchodilability" by subtracting the increase

Table 3. - Peak inspiratory flow (PIF) and forced inspiratory volume (FIV) measured through the Turbuhaler. Statistics are shown for each of the 4 inhalations and for the average of the 4 inhalations.

	PIF (l·min ⁻¹)					FIV (l)				
	Inhalation no				Average of the 4	Inhalation no				Average of the 4
	1	2	3	4		1	2	3	4	
Mean	43	45	46	47	46	1.42	1.54	1.63	1.59	1.59
SD	13	16	16	16	14	0.47	0.64	0.54	0.53	0.53
Min	20	23	23	17	22	0.61	0.57	0.56	0.63	0.79
Max	70	73	78	82	75	2.26	2.78	2.45	2.63	2.47

after Pari Inhalierboy). The PIF and FIV increased slightly after each inhalation, but this was not statistically significant.

The mean (SD) heart rate before/5 minutes after inhalation was 83 (15)/81 (17) (Pari Inhalierboy) and 79 (12)/80 (11) (Turbuhaler). The difference between the heart rate before and after inhalation was not statistically significant.

No side effects were reported from either of the treatments.

Discussion

Clinical trials have found the Turbuhaler equipotent to the terbutaline MDI in children [8] as well as in adults [9, 10]. The two studies on adult patients demonstrated a mean PIF through the Turbuhaler of 68 $l \cdot \text{min}^{-1}$ and 58 $l \cdot \text{min}^{-1}$. One hundred and one asthmatics were found to have a mean PIF through an empty Turbuhaler of 59 $l \cdot \text{min}^{-1}$ (Range: 25–93 $l \cdot \text{min}^{-1}$) [11]. The mean PIF of 46 $l \cdot \text{min}^{-1}$ in the present study was lower, but all the patients were able to create inspiratory flows high enough to use the Turbuhaler, and no significant correlation between PIF or FIV through the Turbuhaler and the maximal increase in FEV₁ or FVC after inhalation was found, when the effect was standardized according to the reversibility of the bronchial obstruction in the individual patient. No "cut off point" for bronchodilation from the Turbuhaler was found in patients with a lung function in the present range. This agrees with results from *in vitro* testing, which have shown that the Bricanyl Turbuhaler, from a total dose of 0.5 mg terbutaline, delivers a respirable fraction (*i.e.* particles with diameters < 5 μm) of 0.12 mg at a linear flow through the mouthpiece of 28.3 $l \cdot \text{min}^{-1}$, and 0.25 mg at a flow of 60 $l \cdot \text{min}^{-1}$ [12]. DOLOVICH *et al.* studied 12 adults with mild to moderate reversible asthma, and found no significant difference with regard to the increase in FEV₁ and FVC after inhalation of one dose of terbutaline from the Turbuhaler at inspiratory flows of 30 $l \cdot \text{min}^{-1}$ and 60 $l \cdot \text{min}^{-1}$. However, inhalation at 60 $l \cdot \text{min}^{-1}$ was found to be more effective in increasing the maximal expiratory flows at 50% and 75% of FVC [13] - these lung function parameters were not measured in the present study.

No significant increase in inspiratory lung function was found between first and last inhalation from the Turbuhaler in the present study, and it therefore appears to be advisable to take successive doses without a pause.

The present study demonstrated no statistically significant differences between the inhalation of 5 mg terbutaline from a Pari Inhalierboy and 2 mg terbutaline from a Turbuhaler. The confidence intervals for the observed differences in the increase in FEV₁ and FVC were sufficiently narrow to ensure that any real differences of clinical importance are unlikely to exist. The FEV₁ and FVC are dependent on the patient's effort and motivation, and the encouragement by the nurse. The appraisal of the two different types of inhalation

by the patient and by the nurse could be a source of bias due to the open design of the study.

The bronchodilating effect obtained by 2 mg terbutaline inhaled through the Turbuhaler was comparable to the effect achieved by 5 mg from the nebulizer. Single doses by each device were studied presently, and the ratio 2:5 cannot directly be applied to other doses, or to other brands of jet nebulizers. It is unlikely that the effects were comparable because the maximal response was obtained by the lower dose (2 mg) of terbutaline from the Turbuhaler, as other investigators have found a linear increase in FEV₁ with doses up to 4 mg terbutaline administered by Turbuhaler [10]. Presumably, the explanation to the comparable effects is that comparable amounts of terbutaline reached the responding airways. A study of 4 common types of jet nebulizer demonstrated that 35–60% of an initial volume of 2 ml stays in the nebulizer as a "dead volume" [14]. The type of nebulizer used in the present study retained about 50% of a 2 ml dose (determined from weight loss of the nebulizing chamber with face mask during inhalation). NEWMAN and PAVIA [15] concluded that, on average about 10% of the dose from nebulizers is delivered to the lungs. The Turbuhaler was found to deliver about 14% of the dose to the lungs in 6 asthmatics with FEV₁ of 28 to 56% of predicted [16].

The evidence for the possibility of replacing nebulizers in the domiciliary treatment of severe airways obstruction is increasing. Terbutaline inhaled from an MDI with a pearshaped extension tube produced more bronchodilation in normal and asthmatic subjects than both nebulizer and conventional MDI when identical doses were compared [17]. Patients with severe airways obstruction were treated as well by MDI (0.2 – 0.6 mg salbutamol 4 times a day) as by nebulizer (2.5 – 5 mg salbutamol 4 times a day) [18]. (These patients had all demonstrated their ability to use the MDI before inclusion in the study). The present study suggests that it will be also possible to replace the domiciliary use of nebulizers with powder inhalations.

The inhalations from the Turbuhaler in the present study were carried out under close surveillance of a nurse. The next step in the evaluation of the Turbuhaler as a replacement for the domiciliary use of a nebulizer in severe chronic airways obstruction is to consider whether these patients can use the powder inhalator on their own and achieve the same effect as they do when using the nebulizer. This is the aim of an ongoing clinical trial.

Acknowledgements: The author wishes to thank Draco Denmark (a subsidiary of AB Astra, Sweden) for supplying the drug under study as well as donating the funds to enable the home visits to be carried out by the nurses. The study was also supported by a grant from the National Association against Lung Diseases.

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Inhalation de poudre de Terbutaline à partir d'un turbuhaler Bricanyl par comparaison avec la Terbutaline en solution pour nébuliseur dans l'obstruction chronique sévère des voies aériennes. N.C.G. Hansen.

RÉSUMÉ: Chez 22 adultes atteints d'une obstruction chronique sévère des voies aériennes (VEMS entre 14 et 57% des valeurs prédites), une comparaison ouverte en permutation croisée a été réalisée à deux jours consécutifs par l'inhalation de 2 mg de poudre de Terbutaline dans un turbuhaler Bricanyl et de 5 mg de Terbutaline administrés par un nébuliseur conventionnel (Pari Inhalierboy). Avant leur inclusion dans l'étude, tous les participants utilisaient la Terbutaline en nébulisation à domicile. L'augmentation maximale moyenne du VEMS dans les 60' après l'inhalation par turbuhaler et par Pari inhalierboy a été respectivement de 27% (SD 15) et de 28% (SD 15). L'augmentation maximale moyenne de la capacité vitale a été de 30% (SD 20) et de 29% (SD 16). Les différences n'ont aucun caractère statistiquement significatif. Tous les patients furent capables de fournir des débits inspiratoires suffisamment élevés pour utiliser le turbuhaler. Cette étude suggère qu'il sera possible de remplacer les nébuliseurs par l'inhalation de poudre, en tout cas en ce qui concerne les effets broncho-dilatateurs.

Eur Respir J., 1989, 2, 716-720