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Terbutaline in COPD Comparison between Turbuhaler® and Chlorofluorocarbon (CFC) Inhaler

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Abstract. Patients with chronic obstructive pulmonary disease (COPD) often subjectively benefit from inhaled β_2-agonists in spite of little or no demonstrable effect in forced expiratory volume in 1 second ($FEV_{1.0}$). A comparison between the effects of terbutaline administered via a dry powder inhaler (Turbuhaler®) and via a chlorofluorocarbon (CFC) inhaler in conjunction with a spacer device (Nebuhaler®) was performed in patients with regard to $FEV_{1.0}$, forced expiratory capacity (FVC), residual volume (RV), and specific conductance (s-Gaw). Fifteen hospitalised patients (11 male) with COPD were studied, each of whom had a diurnal variation in peak expiratory flow (PEF) not exceeding 15% and with a demonstrated volume response to inhaled β_2-agonists in FVC and/or RV of at least 15%. Patients were administered each of the following five treatments on a single occasion in a randomized order (latin square) in intervals of at least 2 days: placebo, terbutaline via Turbuhaler (1.0 and 2.5 mg) and terbutaline via a CFC inhaler (1.0 mg without and 2.5 mg with Nebuhaler). Inhalation of terbutaline in different doses and from different devices induced a decrease in RV, an increase in FVC, and s-Gaw and a less pronounced increase in $FEV_{1.0}$. No statistically significant differences between the four terbutaline treatments were seen, but all were significantly different from the placebo. These findings indicate that while patients with COPD may benefit from inhaled terbutaline through decreased hyperinflation, the choice of inhalation device seems to be of little importance for its efficacy.

Key words: Irreversible airway obstruction—Residual volume—Volume response—Terbutaline—COPD

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Introduction

The degree of improvement in forced expiratory volume in 1 second ($FEV_{1.0}$) or peak expiratory flow (PEF) after inhalation of β_2-agonists is considered essential to differentiate patients with reversible and irreversible airway obstruction. Patients with chronic obstructive pulmonary disease (COPD) have by definition a large irreversible component in airflow limitation [1]. Consequently, they are often discouraged from using β_2-agonists, referring to the lack of increases in $FEV_{1.0}$ and PEF. Lung function measured during tidal breathing undergoes substantial changes after β_2-agonist inhalation in some patients. However, in spite of only small changes in $FEV_{1.0}$ or PEF [2], the decrease in residual volume (RV), the increase in forced vital capacity (FVC), and specific conductance (s-Gaw) may be clinically significant. Patients with severe airflow obstruction increase their respiratory rate even at light physical activity, for example, climbing stairs, etc., which causes an increased hyperinflation [7]. It has been postulated that the hyperinflation could be reduced by the use of inhaled β_2-agonists [5]. The inhalation technique may be of special importance to these patients as their inhalation usually is short and shallow, with a low inspiratory flow. The addition of a spacer (Nebuhaler®) to CFC inhalers has been shown to increase the deposition of inhaled drug in the lung [8]. Therefore, it seems likely that use of devices to improve lung deposition could improve the efficacy of inhaled β_2-agonists, especially in COPD. With advances made in dry powder inhalation devices, new benefits to patients have been offered in terms of administration technique and compliance [10]. As the dry powder inhaler, Turbuhaler has not been studied in COPD patients, this study was designed to compare the effects of lung function of terbutaline inhaled via a CFC inhaler, with or without a spacer (Nebuhaler) and via Turbuhaler.

Patients

Fifteen hospitalised patients (11 male) with severe COPD, all ex-smokers, were included in the study. They were referred from all parts of Sweden to the clinic for optimization of treatment, exercise training, education, and rehabilitation. Their diagnoses were based on thorough clinical history, lung X-ray, spirometry, and body plethysmography after a run-in period of 1 week during which PEF was measured five times a day. Ten of the patients had formerly been labeled "asthmatics" and believed themselves to be suffering from this disease. However, all patients fulfilled the criteria of irreversible airway obstruction and COPD [1] rather than asthma [6]. The patients were in a stable phase without recent exacerbations and their medication was not altered in the weeks prior to or during the study. Their mean basal $FEV_{1.0}$ on the five study days was between 1.0 and 1.1 L. The mean age of the patients was 61 years (range 44–72 yr).

Demographic data and medication are presented in Table 1. Patients were

Table 1. Demographic data

Patent no.	Sex (M/F)	Age (years)	$FEV_{1.0}$ baseline (% of predicted normal value)	Duration of airways disease (yr)	Medication the week prior to start of study
1	M	60	28	32	IB, IS, OS, T, I
2	M	63	24	10	IB, OB, IS, T
3	M	58	46	5	IB, T
4	M	50	47	10	IB, OB, IS, OS, T
5	M	66	37	42	IB, IS, T, I
6	F	56	48	1	IB, OB, IS
7	M	67	23	14	IB, IS, OS
8	M	44	26	7	IB, OB, IS, OS, T, I
9	M	69	25	12	IB, IS, T
10	M	71	23	6	IB, IS, OS, T, I
11	F	55	31	1	IB, IS, OS, T
12	F	58	35	20	IB, IS, T, I
13	M	66	45	4	IB, IS, T
14	F	62	40	4	IB, OB, IS, T
15	M	72	33	6	IB, OB, IS, OS, T
Mean (SD)	11/4	61 (9)	35.6	11.6	
Range		(44–72)	(23–48)	(1–42)	

IB = inhaled β_2-agonist; IS = inhaled steroid; T = oral theophylline (controlled release); OB = oral β_2-agonist; OS = oral steroid; I = Ipratropium bromide.

included if their diurnal PEF variation did not exceed 15% measured from daily recordings during the first week in the hospital. On admission they had demonstrated volume response $\geq$15%, that is an increase in FVC and/or a decrease in RV without concomitant increase (<15%) in $FEV_{1.0}$ after inhalation of a β_2-agonist (four inhalations of either 0.1 mg salbutanol or 0.25 mg terbutaline). Before each study day their medication was withdrawn according to the following schedule: oral β_2-agonists 24 hours, inhaled β_2-agonists 8 hours, oral theophylline drugs and ipratropium bromide 24 hours. Oral and inhaled steroids were allowed if the dose was kept unchanged during the study period.

Materials and Methods

The study was controlled through a double-blind, double-dummy design between treatments 1 and 2 on the one hand and between 3 and 5 on the other hand (see below). After baseline measurements, patients received one of the following five alternative treatments in randomized order (Latin square design) per study day. (1) Terbutaline (1.0 mg = 2 doses of 0.5 mg) via Turbuhaler and placebo CFC inhaler (four doses); (2) Terbutaline (1.0 mg = four doses of 0.25 mg) via a CFC inhaler and placebo Turbuhaler (two doses); (3) Terbutaline (2.5 mg = five doses of 0.5 mg) via Turbuhaler and placebo CFC inhaler with Nebuhaler (ten doses); (4) Terbutaline (2.5 mg = ten doses of 0.25 mg) via a CFC inhaler with Nebuhaler and placebo Turbuhaler (five doses); and (5) Placebo Turbuhaler (five doses) and placebo CFC inhaler with Nebuhaler (ten doses).

All treatments and measurements were performed commencing at 7.30 am on each study day with an interval of at least 48 hours. On each study day the patients underwent lung function measurements using a body plethysmograph (Jaeger Bodyscreen II) with registration of lung volumes (FVC and RV), as well as $FEV_{1.0}$ and s-Gaw before and after medication. The measurements were made 10 minutes before and 5, 20, and 40 minutes after inhalation of the test drug. Data processing was performed using NMSP Version 89 and the statistical analyses by using the statistical standard package SAS (SAS Inc.). Absolute mean values and the change from pretreatment value of each variable on each day were calculated. Comparisons were based on an ANOVA model factored by the patient, treatment, and study day. The following six pairwise comparisons were made: (1) terbutaline via Turbuhaler (1.0 mg) vs terbutaline via a CFC inhaler (1.0 mg); (2) terbutaline via Turbuhaler (1.0 mg) vs terbutaline Turbuhaler (2.5 mg); (3) terbutaline via a CFC inhaler (1.0 mg) vs terbutaline CFC inhaler and Nebuhaler (2.5 mg); (4) terbutaline via Turbuhaler (2.5 mg) vs terbutaline via a CFC inhaler and Nebuhaler (2.5 mg); (5) terbutaline via Turbuhaler (2.5 mg) vs placebo; and (6) terbutaline via a CFC inhaler and Nebuhaler (2.5 mg) vs placebo.

Results

All patients completed the measurements on the study days except during the placebo day. Six patients deteriorated and could not refrain from using their own inhaled β_2-agonist. One patient dropped out directly, one after 5 minutes and four 20 minutes after the pretreatment measurement. (Nine patients completed all measurements).

Figure 1 and Table 2 show, for all five treatments, the mean changes in $FEV_{1.0}$, FVC, and RV from pre- to posttreatment.

$FEV_{1.0}$

Mean pretreatment values of $FEV_{1.0}$ were between 32 and 36% of predicted normal values of the five study days. All active treatments resulted in an increase in $FEV_{1.0}$ but not the placebo. However, no statistically significant differences were seen between the active treatments. The individual responses are shown in Fig. 2. The differences between terbutaline via Turbuhaler (2.5 mg) and the CFC inhaler (2.5 mg) vs placebo were statistically significant, ($p < 0.001$).

FVC

Mean pretreatment values ranged between 71 and 75% of predicted normal values. All active treatments resulted in an increase in FVC. No statistically significant differences were seen between the active treatments. The differences between terbutaline via Turbuhaler (2.5 mg) and the CFC inhaler (2.5 mg) vs placebo were statistically significant, ($p < 0.001$).

RV

All active treatments resulted in a decrease in RV, with no statistically significant differences between the active treatments. The individual responses to

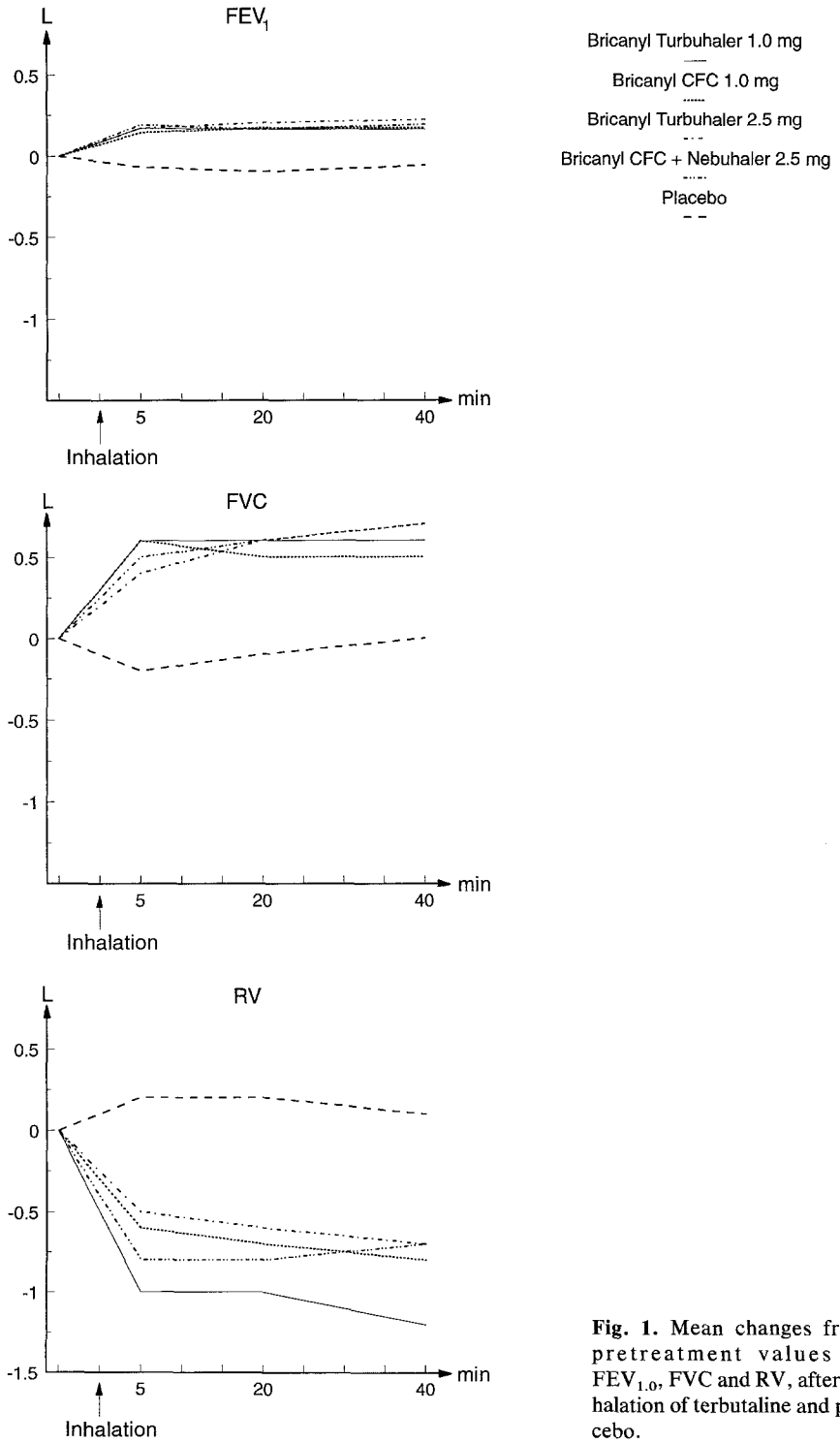

Fig. 1. Mean changes from pretreatment values of $FEV_{1.0}$, FVC and RV, after inhalation of terbutaline and placebo.

Table 2. Mean pretreatment values and changes from baseline 40 minutes after inhalation of the study medication

Treatment	$FEV_{1.0}$ (L)		FVC (L)		RV (L)		s-Gaw $(kPa/L/S)^{-1}$	
	Mean (SD)	Change (SD)	Mean (SD)	Change (SD)	Mean (SD)	Change (SD)	Mean (SD)	Change (SD)
Bricanyl CFC 1.0 mg	1.0 (0.3)	0.2 (0.1)	2.8 (1.0)	0.5 (0.4)	4.4 (1.2)	−0.8 (0.9)	0.38 (0.26)	0.13 (0.18)
Bricanyl Turbuhaler 1.0 mg	1.1 (0.4)	0.2 (0.1)	2.8 (1.0)	0.6 (0.4)	4.8 (1.4)	−1.2 (0.8)	0.40 (0.26)	0.17 (0.14)
Bricanyl CFC 2.5 mg	1.1 (0.4)	0.2 (0.2)	2.9 (0.9)	0.7 (0.5)	4.3 (1.6)	−0.7 (1.0)	0.43 (0.29)	0.21 (0.22)
Bricanyl Turbuhaler 2.5 mg	1.1 (0.4)	0.2 (0.2)	3.0 (0.9)	0.7 (0.4)	4.3 (1.7)	−0.7 (0.7)	0.44 (0.26)	0.23 (0.25)
Placebo	1.1 (0.3)	−0.1 (0.1)	2.8 (0.8)	0 (0.4)	4.2 (1.2)	0.1 (0.3)	0.39 (0.23)	−0.05 (0.09)

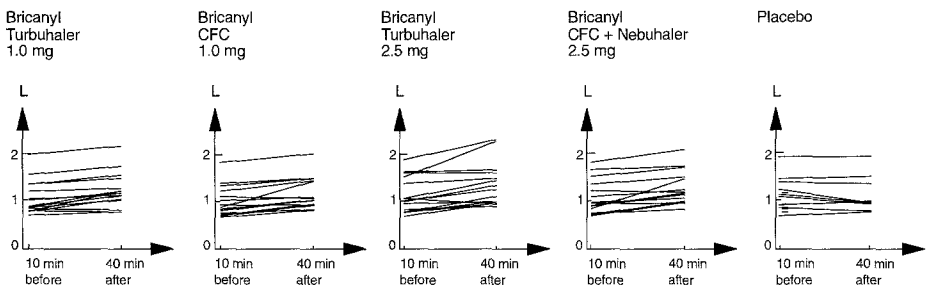

Fig. 2. Individual responses in $FEV_{1.0}$ to two doses of terbutaline administered via three different inhalation devices in comparison to placebo before and 40 minutes after inhalation.

the treatments are shown in Fig. 3. The differences between terbutaline via Turbuhaler (2.5 mg) and the CFC inhaler (2.5 mg) vs placebo were statistically significant, ($p < 0.01$ and $p < 0.05$, respectively).

s-Gaw

All active treatments resulted in an increase in s-Gaw (Table 2 and Fig. 4). Like the former variables, no statistically significant differences were seen between the active treatments. The differences between terbutaline via Turbuhaler (2.5 mg) and the CFC inhaler (2.5 mg) vs placebo were statistically significant, ($p < 0.001$). The only adverse event observed was coughing. Six patients deteriorated in their breathlessness after the placebo inhalation and could not refrain from using their own β_2-agonist inhaler for relief. For these patients the 40 minutes posttreatment reading was not obtained.

Discussion

The study focused on two issues. The first issue was whether a bronchodilator response, expressed as an increase in $FEV_{1.0}$, is a major determinant if an inhaled bronchodilator is or is not to be prescribed [4]. During the study days a small response in $FEV_{1.0}$ to inhaled terbutaline was observed in some patients. However, this response was of less magnitude than the volume response, that is, the changes in FVC and RV. Thus, this study confirms that selected COPD patients can improve by "volume response" to inhalation of β_2-agonists [2]. Furthermore s-Gaw, also increased after terbutaline in contrast to placebo, which indicates that there is a direct effect on the bronchial muscles. The fact that the six patients who deteriorated were all on placebo indicates that β_2-agonists have a protective effect. However, it is well known that any cause of increased effort of breathing in severe COPD induces a rise in respiratory rate and FRC [7]. Thus, the deterioration could have been caused by bronchial hyperresponsiveness and the frequent inhalations of placebo (both

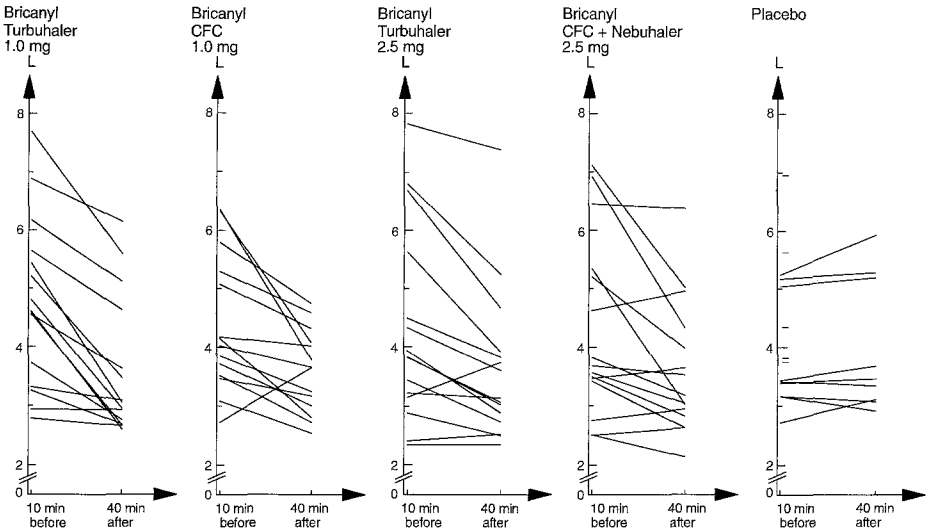

Fig. 3. Individual responses in RV to two doses of terbutaline administered via three different inhalation devices in comparison to placebo before and 40 minutes after inhalation.

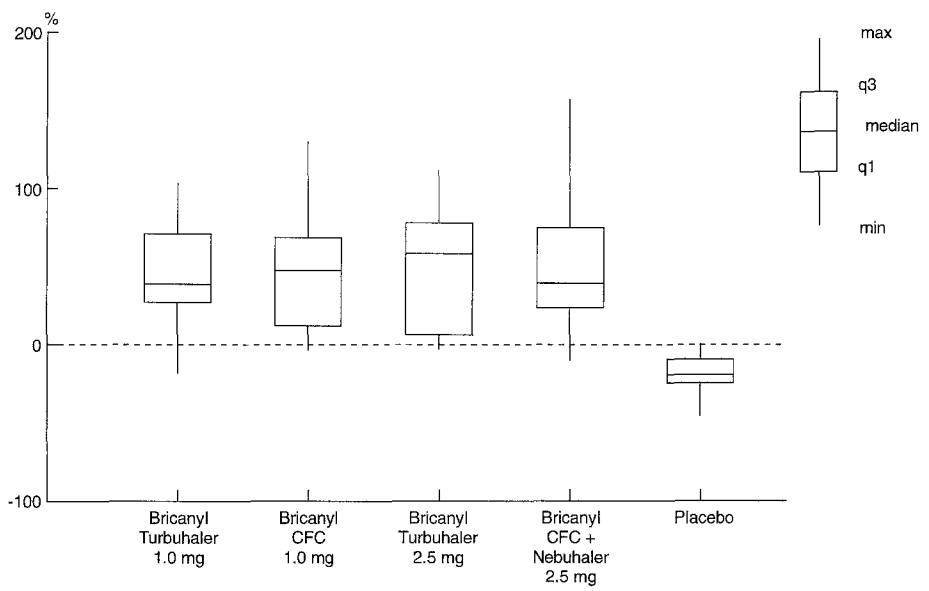

Fig. 4. Changes from pretreatment value in specific conductance (s-Gaw) during tidal breathing 20 minutes after terbutaline and placebo.

via Turbuhaler and the CFC inhaler) or the repeated lung function measurements may have provoked bronchoconstriction.

The second issue was whether there were any differences in efficacy between the powder inhaler, Turbuhaler, and the conventional CFC inhaler with and without a spacer. Inhalation via the CFC inhaler is more difficult to per-

form, due to the need of synchronisation of inhalation and actuation than via Turbuhaler, which is an inspiratory flow-driven inhaler. However, this study showed no difference in the response to terbutaline inhaled via the different devices. Theoretically, the use of a spacer should improve the efficacy of a CFC inhaler in COPD patients. However, we could not find any such difference in neither bronchodilating effect nor volume response between inhalation of terbutaline via Turbuhaler or via a CFC inhaler with Nebuhaler. An explanation of the lack of differences between the devices or dose responses may be that a maximal effect was rapidly reached irrespective of studied dose and device.

There is no standardized norm for how to describe the response of a bronchodilator [9]. The most common way is to express the response as a change in percentage of initial $FEV_{1.0}$. If the increase is less than 15%, the obstruction is usually described as irreversible. However, such a threshold is not an accurate discriminator between asthmatic patients and those with COPD [9]. In patients with a clinical history of asthma, inhaled β_2-agonists will usually be prescribed irrespective of the reversibility performance. In patients with COPD, however, a negative reversibility test may discourage the doctor from prescribing inhaled β_2-agonists. This may result in undertreatment and, furthermore, more limitations in physical activity than necessary. Although the therapeutic benefit of long-term use of inhaled β_2-agonists has been under debate, many patients with COPD show clinical improvement, often with regard to breathlessness and in exercise dyspnoea during such treatment [5]. COPD patients with these subjective improvements from inhaled β_2-agonists will most likely respond with increased FVC and decreased RV. The reduced degree of hyperinflation may thus diminish their dyspnoea and improve their quality of life.

In conclusion, COPD patients with "irreversible" airway obstruction as judged by $FEV_{1.0}$ response may benefit from inhalation of β_2-agonists by volume response. The choice of inhalation device seems to be of little importance for the efficacy.

Acknowledgment. Informed consent was obtained. The study was approved by the regional Ethics Committee at the University of Umeå.

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