RESPIRATORY MEDICINE (1998) **92**, 167–172

β_2-agonists administered by a dry powder inhaler can be used in acute asthma

A. NANA*, P. YOUNGCHAIYUD*, N. MARANETRA*, J. BOE†, C-G. LÖFDAHL‡, O. SELROOS§ AND E. STÅHL§

*Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
†Department of Respiratory Medicine, Rikshospitalet, Oslo, Norway
‡Department of Respiratory Medicine, University Hospital, Lund, Sweden
§Astra Draco AB, Lund, Sweden

Patients with acute asthma attending the emergency room were included in a double-blind, double-dummy and parallel group study to investigate whether a dry powder inhaler (Turbuhaler®) can be used in acute asthma. If so, the aim was to establish the potency relationship between a β_2-agonist (salbutamol) administered by the dry powder inhaler and the pressurized metered-dose inhaler (pMDI).

Eighty-six patients with a mean age of 38 years and forced expiratory volume in 1 s (FEV_1) of 37% of predicted normal value were randomized at Siriraj Hospital in Bangkok to either Turbuhaler (50 μg dose^{-1}) or pMDI (100 μg dose^{-1}) with spacer (Volumatic®). Doses of 100+300+300+300 μg salbutamol were given at 0, 15, 30 and 45 min via Turbuhaler and repeated at 90, 105, 120 and 135 min (total dose 2000 μg). The same inhalation schedule with identical number of doses was used for the pMDI with spacer but in double doses (total 4000 μg), assuming a dose–potency ratio of salbutamol administered via Turbuhaler compared with the pMDI of 2:1. At 85 min after the first dose, 60 mg prednisolone was given orally. FEV_1 was measured 10 min after each dosing. Peak inspiratory flow (PIF) through Turbuhaler was measured on each dosing occasion. Plasma (P)-salbutamol, serum (S)-potassium concentrations, pulse rate, blood pressure and adverse events were recorded.

No statistically significant differences were observed in the increase in FEV_1 between the groups: 55 min (165 min) after the first dose, the increase was 0·47 l and 47% (0·64 l and 63%) in the Turbuhaler group, and 0·46 l and 42% (0·68 l and 65%) in the pMDI group. Mean PIF though Turbuhaler was 49 l min^{-1} (range 26–68) at first inhalation and increased to 60 l min^{-1} (range 38–86). There was no correlation between the initial PIF through Turbuhaler and the initial FEV_1 response. P-salbutamol and S-potassium values correlated well. A larger decrease in S-potassium was noticed after 75 min in the pMDI group (0·38 mmol l^{-1}) compared with the Turbuhaler group (0·23 mmol l^{-1}) (P=0·02).

In conclusion, the use of a dry powder inhaler, Turbuhaler, was investigated in the emergency room treatment of acute asthma, and was as effective as a pMDI with spacer. Half the dose of salbutamol administered via Turbuhaler was as effective as the full dose given via a pMDI with spacer.

RESPIR. MED. (1998) **92**, 167–172

Introduction

Inhaled β_2-agonists given by pressurized metered-dose inhalers (pMDI) or nebulizers are well established in the treatment of acute asthma and other obstructive airway diseases (1). They are associated with a rapid onset of action, good efficacy at low doses and few adverse events. Salbutamol is a relatively selective β_2-agonist which has been on the market for several years. Treatment with nebulized short-acting β_2-agonists is still the most used treatment in patients with acute asthma (2). Inhalation via a pMDI with spacer has also been shown to be effective and is a well-established method of delivering the drug directly to the airways in patients with acute asthma (3–5). The use of pMDIs, however, has some drawbacks, as they require propellants and lubricants to operate accurately, and these additives may cause or increase bronchospasm in some asthmatic individuals (6–8).

Turbuhaler® is an inspiratory-flow-driven, multi-dose, dry powder inhaler developed by Astra Draco AB, Sweden, for administration of drugs to the lungs (9). Recently, efficacy studies in patients with stable asthma have indicated that half the dose of salbutamol via pMDI is required

Received 11 December 1996 and accepted in revised form 4 March 1997.
Correspondence should be addressed to: E. Ståhl, Astra Draco AB, P.O. Box 34, S-221 00 Lund, Sweden.

0954-6111/98/020167+06 $12.00/0

via Turbuhaler to achieve the same bronchodilating response (10,11). This 2:1 relationship in lung efficacy has also been shown for terbutaline (12) and budesonide (13). Lung deposition data support this dose–potency relationship (12). This is in line with the findings recently published that asthmatic patients with acute asthma performed significantly better when the same dose of terbutaline was administered via Turbuhaler than via pMDI and spacer (Nebuhaler®) (14).

The objective of this study was to investigate whether the dry powder inhaler can be used in acute asthma and, if so, to establish the potency relationship between salbutamol Turbuhaler and salbutamol pMDI and spacer (Volumatic).

Methods

PATIENTS

A total of 86 Thai asthmatic patients, attending the emergency room (ER) at Siriraj Hospital in Bangkok, Thailand, were enrolled into the study between September 1994 and July 1995. The inclusion criteria were: (i) age between 16 and 50 years; (ii) FEV_1 between 20 and 50% of predicted normal value; and (iii) a pulse rate of more than 100 beats min^{-1} adopting criteria used in earlier studies of acute asthma (15–17). The study protocol was approved by the Ethics Committee at Siriraj Hospital. Each patient gave signed informed consent before the start of the study. The study was conducted in accordance with the principles stated in the Declaration of Helsinki and according to FDA Regulations and Guidelines of Good Clinical Practice.

DESIGN

The study was of a randomized, double-blind, double-dummy parallel group design. Demographic data and asthma therapy taken within 24 h before arrival at the ER, as well as current therapy, were recorded. Oxygen therapy was given to all patients during the study via a nasal prong. Inhalation technique was standardized for the two inhalers according to the manufacturers' recommendation. The inhalers were primed prior to the start of the procedures, and the spacer was primed with a placebo in order to reduce static charge.

The patients were randomized to either salbutamol Turbuhaler ($50\,\mu g\,dose^{-1}$) or salbuterol pMDI ($100\,\mu g\,dose^{-1}$). Doses of $100+300+300+300\,\mu g$ salbutamol were given at 0, 15, 30 and 45 min via Turbuhaler and repeated at 90, 105, 120 and 135 min (total dose $2000\,\mu g$). The same inhalation schedule with an identical number of doses was used for the pMDI with spacer but in double doses (total $4000\,\mu g$), assuming a dose–potency ratio of salbutamol administered via Turbuhaler compared with the pMDI of 2:1. At 85 min after the first dose, 60 mg prednisolone was given orally [Fig. 1(a)]. FEV_1 was measured 10 min after each dose of albuterol, at 75 min and at the completion of the study (165 min) [Fig. 1(b)]. Blood samples were taken before and 75 and 165 min after the study start.

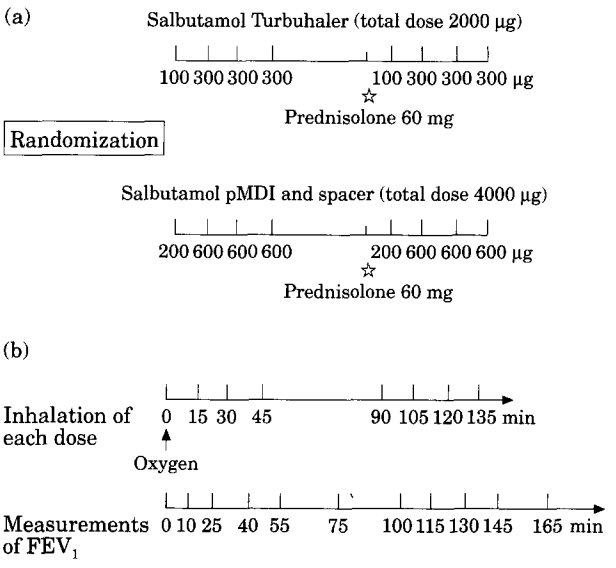

FIG. 1. (a) Randomization schedule. (b) Inhalation schedule and time of measurements of forced expiratory volume in 1 s (FEV_1).

MEASUREMENTS

FEV_1 was obtained in a sitting position using the Vitalograph® Alpha spirometer (Vitalograph Ltd, U.K.). Before the spirometry test was performed (best of three measurements, if possible), pulse rate (beats min^{-1}) and blood pressure (mmHg) were measured, possible adverse events were recorded, and blood samples were taken for analysis of serum (S)-potassium and plasma (P)-salbutamol. At the first inhalation on each dosing occasion via Turbuhaler and via pMDI with spacer, peak inspiratory flow (PIF) through the inhalers was measured by connecting Turbuhaler and the pMDI with spacer to Vitalograph MDI Modified Compact (Vitalograph Ltd, U.K.). A subjective question on clinical symptoms ('How is your asthma now?') using a visual analogue scale (VAS: 0–100 where 0=no symptoms and 100=severe symptoms) was included. S-potassium was analysed at the Bioanalytical Chemistry Department, Astra Draco AB, using COMBAS, MIRA PLUS, Serial No. 30-5929, Roche Diagnostics, Basel, Switzerland. The concentration of P-salbutamol was determined by a gas chromatography–mass spectrometry method at the Bioanalytical Chemistry Department (18).

STATISTICAL ANALYSIS

The primary efficacy variable was the 55-min measurement of FEV_1, which was compared between the groups, using the baseline measurement as covariate in an ANOVA. The model is multiplicative, so the logarithm of both variables was used in the analysis. For descriptive purposes, the ratio of the 55-min measurement over the entry measurement (baseline) was used as effect variable. The adjusted percentage increase from baseline was obtained by exponentiating back to the original scale.

TABLE 1. Baseline characteristics of patients

Characteristics	Turbuhaler® (n=43)	pMDI and spacer (n=43)
Age (years)	40 (16–49)	37 (16–49)
Sex (M/F)	14/29	18/25
Current smokers (no.)	3	5
Duration of asthma (years)	17 (1–42)	19 (1–40)
FEV_1 (l)	0·88 (0·37–1·35)	0·92 (0·42–1·53)
% predicted	37·5 (20–49)	36·3 (20–49)
Pulse rate (beats min^{-1})	108 (101–122)	108 (102–136)
BP (mmHg) systolic/diastolic	126/81	129/84
Clinical symptoms (visual analogue scale, 1–100)	69 (25–96)	70 (31–96)
PIF through Turbuhaler (l min^{-1})	49 (26–68)	47 (21–77)
PIF through pMDI and spacer (l min^{-1})	18 (7–33)	16 (6–32)

Values of continuous variables are expressed as mean (range).
PIF, peak inspiratory flow; pMDI, pressurized metered-dose inhaler.

Systemic effect variables (pulse rate, blood pressure and S-potassium) were analysed in the same way, except that additive models were used.

In addition, a few other time points were analysed in the same way (10-min and 165-min value of FEV_1, 75-min and 165-min value of S-potassium).

With 40 evaluable patients in each group, there was an 80% chance of detecting a difference in the increase in FEV_1 that was at least 62% of the standard deviation. With a standard deviation of 0·4 l, a difference of 0·25 l would be detectable. This assumes a two-sided significance level of 5%.

Results

STUDY POPULATION

In total, 86 patients (54 women) were enrolled and randomized, and all were evaluable. Their mean age was 38 years (range 16–49). Table 1 shows the baseline characteristics in the two groups. Of the 86 patients, 30 used inhaled steroids, 49 patients used oral β_2-agonists and 48 patients used xanthines as concomitant medication. The two treatment groups were comparable with regard to the concomitant medication.

One patient, randomized to the pMDI group, discontinued due to worsening of airway symptoms after taking the dose given at 45 min. FEV_1 measurement at 55 min and S-potassium at 75 min were taken and these values are included in the analysis.

SPIROMETRY

Both groups markedly improved in lung function over time. The mean increase of FEV_1 from baseline to 55 min after first dose was 0·47 l (47%) in the Turbuhaler group and 0·46 l (42%) in the pMDI group. Figure 2 shows the FEV_1 values at each time point. There was no statistically significant difference between the groups at any time point [95% confidence interval (C.I.): −7, −15%]. Ten minutes after the first dose, the mean increase was 23% in the Turbuhaler group and 19% in the pMDI group. At the end of the study (165 min after the first dose), the increase was 63% in the Turbuhaler group and 65% in the pMDI group, ranging from 19 to 158%. An analysis also showed that the increase in FEV_1 was not significantly dependent on the duration of asthma.

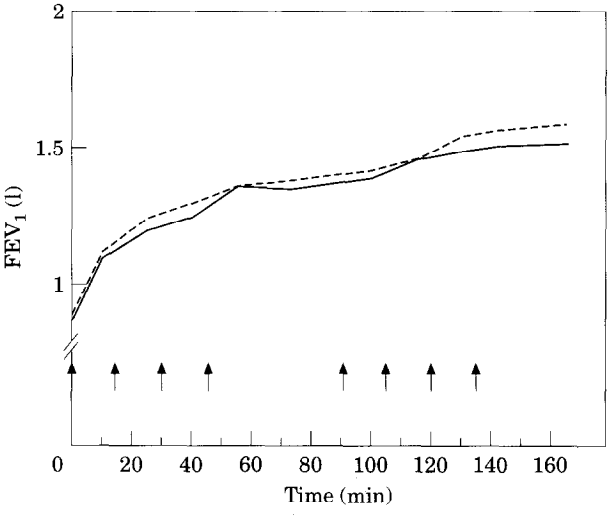

FIG. 2. Absolute mean values of forced expiratory volume in 1 s (FEV_1) with time. ——, Turbuhaler; – – –, pressurized metered-dose inhaler. Arrows indicate dosing time.

The mean values of PIF through Turbuhaler were 49 l min^{-1} (range 26–68) at first inhalation and increased to 60 l min^{-1} (range 38–86) at the last inhalation. The correlation was not statistically significant between the initial PIF through Turbuhaler and the initial FEV_1 response (Fig. 3). The initial mean values of PIF through

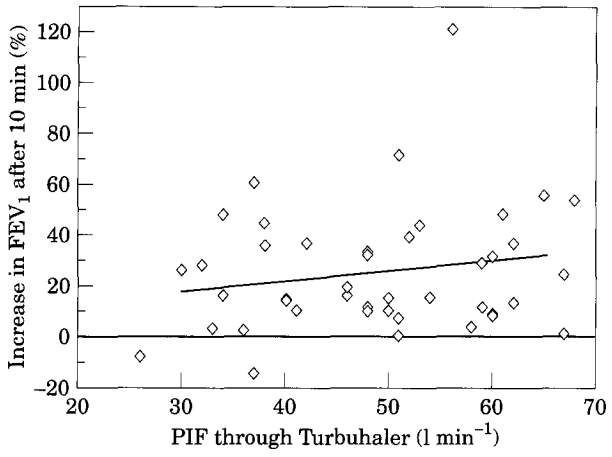

FIG. 3. Correlation between initial peak inspiratory flow (PIF) through Turbuhaler® and initial forced expiratory volume in 1 s (FEV_1) response.

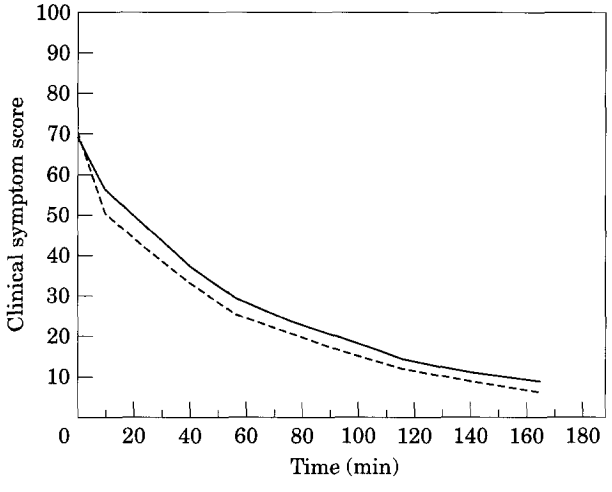

FIG. 4. Mean values of clinical symptoms (0=no symptoms, 100=severe symptoms). ——, Turbuhaler; – – –, pressurized metered-dose inhaler.

pMDI with spacer were 16 l min^{-1} (range 6–32) and 21 l min^{-1} (range 6–30) at the last inhalation.

SYMPTOMS

Clinical symptom scores on the VAS decreased in both treatment groups. The baseline variables were, on average, 70 in both groups; at 165 min, the values were 8 in the Turbuhaler group and 6 in the pMDI group. Figure 4 shows the effect with time, which was statistically significant in both groups without any significant difference between the two groups. A correlation with FEV_1 was observed with a slope of −0·60 with 95% C.I. of −0·75 and −0·46.

SYSTEMIC EFFECTS

There was a decrease in pulse rate and blood pressure during the study period with no statistically significant

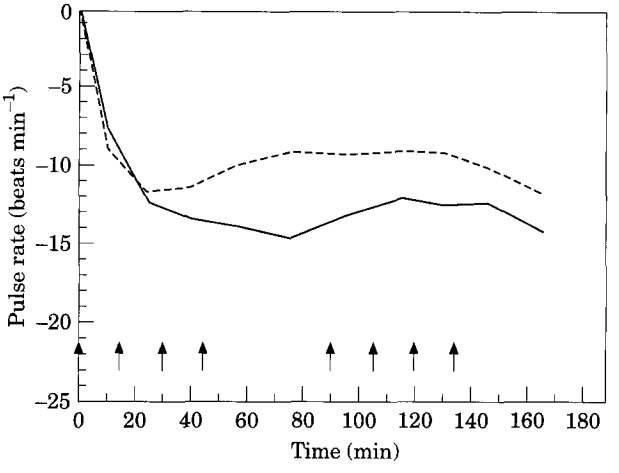

FIG. 5. Mean values of the decrease in pulse rate. ——, Turbuhaler. – – –, pressurized metered-dose inhaler. Arrows indicate dosing time.

difference between the groups. Figure 5 shows the decrease in pulse rate with time. The mean baseline value of S-potassium was 4·01 mmol l^{-1} in the Turbuhaler group and 4·11 mmol l^{-1} in the pMDI group. After 75 min, S-potassium in the pMDI group had decreased by 0·38 mmol l^{-1} compared with 0·23 mmol l^{-1} in the Turbuhaler group. The difference, 0·16 mmol l^{-1}, has 95% C.I. of 0·02 and 0·29 (P=0·02). At the end of the study, 165 min after the first dose, the total decrease was 0·48 mmol l^{-1} with pMDI with spacer and 0·40 mmol l^{-1} with Turbuhaler. The difference was not statistically significant.

A number of patients entered with significant amounts of measurable salbutamol in plasma. Looking at the median increase, the P-salbutamol increased from 8·1 pmol l^{-1} (baseline) to 19·5 pmol l^{-1} (75 min) and to 32·7 pmol l^{-1} (165 min) in the Turbuhaler group. The corresponding values were 11·0, 28·4 and 42·0 pmol l^{-1} in the pMDI group.

The level of S-potassium correlated well with the plasma concentration of salbutamol (a slope of −0·020, C.I. −0·022 and −0·017) so that higher P-salbutamol corresponded to lower S-potassium [Fig. 6(a)]. Pulse rate was also shown to correlate inversely with P-salbutamol with the slope of −0·47 (C.I. −0·61, −0·35). This shows that the increased concentrations of salbutamol did not result in a higher pulse rate [Fig. 6(b)].

Two adverse events (both headache) were reported by one patient in each treatment group. No serious adverse events were reported.

Discussion

The present study showed that a dry powder inhaler can be used in the treatment of patients with acute asthma, together with oxygen and high doses of systemic steroids, as suggested in recent guidelines (19). In addition, it was seen that salbutamol inhaled via Turbuhaler was as effective as

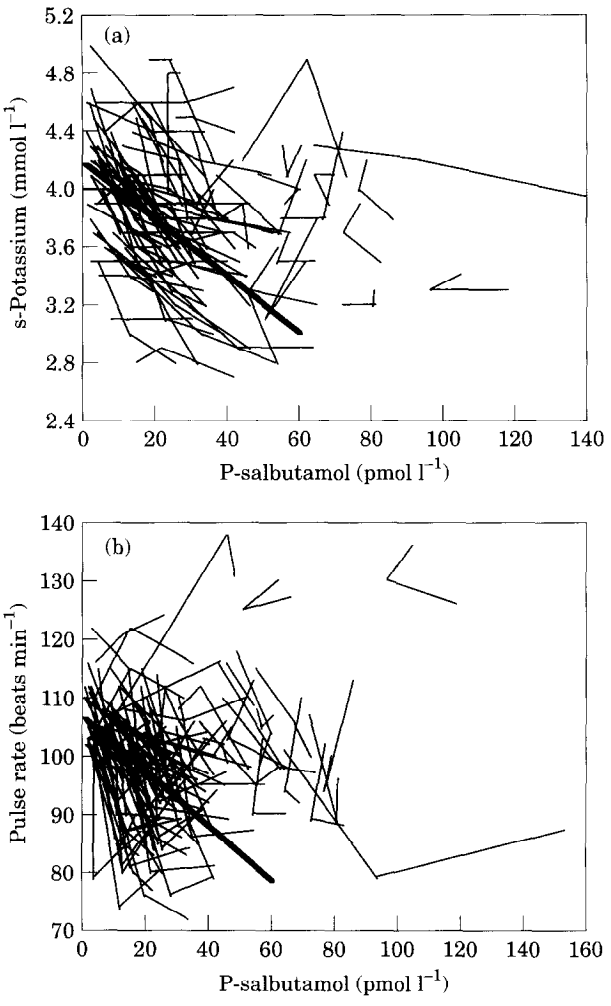

FIG. 6. Correlation between P-salbutamol and (a) S-potassium, and (b) pulse rate.

salbutamol via pMDI with spacer, but at half the dose. In the present study, a total of 4 mg was given by multiple actuations via pMDI according to the guidelines on management of acute asthma (19). This corresponds to half the dose given via Turbuhaler (2 mg). The differences in effect between Turbuhaler and pMDI were very small and were not statistically significant; thus both administrations can be considered to be equally effective in improving lung function. These results are in accordance with another study performed in acute asthma comparing terbutaline inhaled via Turbuhaler and via pMDI and spacer (14). In that study, the nominal doses were the same via both devices.

The present results also support recently published reports in stable asthma showing that the same bronchodilating response can be achieved with half the dose of salbutamol given by Turbuhaler compared with pMDI (10,11). Another study has shown that the lung deposition after Turbuhaler inhalation is twice the lung deposition after a pMDI inhalation. This relationship was also reflected in the efficacy measured as FEV_1 (12).

In the present study, a plateau seemed to have been reached with regard to bronchodilatation after inhalation of half the total salbutamol dose. However, after inhaling the remaining doses, a further increase occurred. This increase may be due to the improved delivery of the subsequent doses because of widening of the airways. Another explanation may, of course, be that the increase was due to the dose of oral prednisolone given after half the total salbutamol dose; 35 min after oral prednisolone, the further increase occurred. Similar findings have been published showing that prednisolone given as a single dose intravenously restored responsiveness to inhaled β_2-agonists (20). However, these findings were obtained 1 h after the prednisolone was given.

The subjective judgement of the patients condition measured by a VAS appeared to be similar in the two groups. A correlation with the objective measures of FEV_1 was observed. However, the clinical symptoms were almost at zero at completion of the study, whereas the FEV_1 was, on average, 64% of predicted in both groups. Once again, this discrepancy confirms the difficulty patients have in estimating their actual degree of airway obstruction, and stresses that objective measurements are essential for evaluating therapeutic success in the treatment of acute asthma.

Mean PIF through Turbuhaler at the study inclusion was 50 l min^{-1} and slightly lower than in another study in patients with acute asthma (21). PIF through Turbuhaler increased by time up to 60 l min^{-1} which could be a learning effect, but could also be an indication of a therapeutic response. The values of PIF through Turbuhaler in patients during the stable phase of the asthma disease have been shown to be between 50 and 60 l min^{-1}, which is comparable with the values in the present study (22)). It has been of some concern whether patients with deteriorating asthma and low FEV_1 produce sufficient inspiratory effort in order to obtain an appropriate dose from Turbuhaler. In this study, no statistically significant increase in response was seen with higher PIF. Many patients clearly has a large response even when inhaling through Turbuhaler with a PIF of less than 50 l min^{-1}. This means that patients with decrease in lung function due to acute asthma are able to benefit from drugs inhaled via Turbuhaler.

Pulse rate, systolic and diastolic blood pressure and S-potassium were assessed as markers of systemic drug effects. On pulse rate and blood pressure, small systemic effects were seen and no treatment difference was detected. Pulse rate decreased by 10–12 beats min^{-1} after the first two doses and remained at that level. The high doses of β_1-agonists given did not further affect the pulse rate at the end of the study. This is in accordance with a study performed by Jansen and Herala (23). In that study, significant increase in lung function was noticed without significant changes in pulse rate, respiratory rate or tremor. This can be explained by the fact that patients with acute asthma have a high sympathetic drive, which decreases after treatment and thereby masks any systemic side-effects the treatment may have.

There was a slightly greater effect on S-potassium when salbutamol was given by pMDI with spacer as compared with the administration by Turbuhaler. However, the

P-salbutamol values correlated well with S-potassium in contrast to a study where plasma concentration in relation to the β_2-agonist intake was studied (24).

In conclusion, the use of a dry powder inhaler such as Turbuhaler was investigated in the emergency room treatment of acute asthma, and was as effective as a pMDI with spacer. Half the dose of salbutamol via Turbuhaler was as effective as the full dose given via pMDI with spacer.

References

1. National Heart, Lung and Blood Institute, National Institutes of Health. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992; **5:** 601–641.
2. Crompton GK. Nebulized or intravenous β_2-adrenoceptor agonist therapy in acute asthma. *Eur Respir J* 1990; **3:** 125–126.
3. Turner JR, Corkery RRT, Eckman D, Gelb AM, Lapavasky A, Shepperd D. Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute airflow obstruction. *Chest* 1988; **93:** 476–481.
4. Morgan MDL, Singh BV, Frame MH, Williams SJ. Terbutaline aerosol given through pear spacer in acute severe asthma. *Br Med J* 1982; **285:** 849–850.
5. Permpikul C, Youngchaiyud P, Charoenratanakul S. Treatment of acute severe asthma with inhaled low dose terbutaline or subcutaneous adrenaline. *Thai J Tuberc Chest Dis* 1990; **11:** 183–191.
6. Selroos O, Löfroos AB, Pietinalho A, Riska H. Comparison of terbutaline and placebo from a pressurised metered dose inhaler and a dry powder inhaler in a subgroup of patients with asthma. *Thorax* 1994; **49:** 1228–1230.
7. Engel T. Patient-related side effect of CFC propellants. *J Aer Med* 1991; **4:** 163–167.
8. Jackson L, Ståhl E, Holgate ST. Terbutaline via pressurized metered dose inhaler (pMDI) and Turbuhaler® in highly reactive asthmatic patients. *Eur Respir J* 1994; **7:** 1598–1601.
9. Wetterlin K. Turbuhaler® – a new powder inhaler for administration of drug to the airways. *Pharm Res* 1988; **5:** 506–508.
10. Löfdahl CG, Andersson L, Bondesson E *et al.* Albuterol doses inhaled via Turbuhaler® gives a better bronchodilating effect than when given via pressurized metered dose inhaler. *Eur Respir J* 1994; **7** (Suppl. 18): 49s.
11. Chapman K, Friberg K, Balter M *et al.* Albuterol via Turbuhaler versus albuterol via pressurized metered-dose inhaler in asthma. *Ann Allery* 1997; **78:** 59–63.
12. Borgström L, Derom E, Ståhl E, Wåhlin-Boll E, Pauwels R. Increased effect of terbutaline Turbuhaler® versus pMDI is related to degree of lung deposition. *Am J Respir Crit Care Med* 1996; **153:** 1636–1640.
13. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993; **69:** 130–133.
14. Tönnesen F, Laursen LC, Evald T, Ståhl E, Ibsen T. Bronchodilating effect of terbutaline powder in acute severe bronchial obstruction. *Chest* 1994; **105:** 697–700.
15. Swedish Society of Chest Medicine. High-dose inhaled versus intravenous salbutamol combined with theophylline in severe acute asthma. *Eur Respir J* 1990; **3:** 125–126.
16. Youngchaiyud P, Charoenratanakul S, Nana A, Wong E, Laxmyr L, Bamberg P. Intravenous enprofylline in the treatment of patients with acute asthma. *J Int Med Res* 1990; **18:** 473–482.
17. Youngchaiyud P, Charoenratanakul S. Terbutaline pressurized aerosol inhaled via Nebuhaler – an effective alternative to subcutaneous adrenaline for treatment of acute severe asthma. *Eur J Respir Dis* 1987; **70:** 284–292.
18. Leferink JG, Dunkers J, Maes RA. A time-saving method for the determination of the β_2-sympathomimetics terbutaline, salbutamol and fenoterol. *J Chromatogr* 1982; **229:** 217–221.
19. British Thoracic Society, Research Unit of the Royal College of Physicians of London, Kings Fund Centre, National Asthma Campaign. Guidelines on the management of asthma in adults II-acute severe asthma. *Br Med J* 1990; **301:** 797–780.
20. Ellul-Micallef R, Fenech FF. Effect of intravenous prednisolone in asthmatics with diminished adrenergic responsiveness. *Lancet* 1975; **11:** 1269–1270.
21. Brown PH, Ning ACWS, Greening AP, McLean A, Crompton GK. Peak inspiratory flow through Turbuhaler® in acute asthma. *Eur Respir J* 1995; **8:** 1940–1941.
22. Engel T, Heinig JH, Madsen F, Nikander K. Peak inspiratory flow and inspiratory vital capacity of patients with asthma measured with and without a newly dry powder inhaler device (Turbuhaler®). *Eur Respir J* 1990; **3:** 1037–1041.
23. Jansen C, Herala M. Plasma terbutaline levels in nebulisation treatment of acute asthma. *Pulm Pharmacol* 1991; **4:** 135–139.
24. Boe J, Ljungholm K. Drug intake and plasma concentration in acute asthma. *Respiration* 1984; **45:** 430–438.