

Turbuhaler®: a new device for dry powder terbutaline inhalation

C. R. JOHNSEN & E. RUNG WEEKE

Clinic of Allergy, County Hospital, Roskilde, Denmark

The aim of this study was to compare bronchodilator response and adverse effects of terbutaline when administered with the metered dose inhaler (MDI) Bricanyl® and with the dry powder inhaler Bricanyl Turbuhaler® (BT). Nine adult patients with bronchial asthma participated. The study was of an open crossover design. At 30-min intervals the patients inhaled increasing doses of terbutaline (0.25 mg to 5.0 mg cumulated) from either the conventional MDI or from the BT. After each inhalation FEV₁, FVC, heart rate, muscle tremor and adverse effects were recorded. Both treatments, BT and MDI, resulted in a dose-related increase in lung function, without any statistical difference. Taste sensation, muscle tremor and increase in heart rate were observed in both groups. Because of the design of the BT one may assume that inhalation failure can be avoided.

Key words: asthma; dose-response study; dry powder inhalator; terbutaline.

Accepted for publication 15 March 1988

The β_2 -selective bronchodilator properties of terbutaline when administered with a metered dose inhaler have been well established (1, 2). It is an effective method of delivering the drug to the large surface area of the tracheobronchial tree. The drawback of the MDI is their content of fluorocarbonated propellants (Freones - CFCl₃, CF₂Cl₂, C₂F₄Cl₂) (6), lubricants (sorbitan trioleate or oleic acid), or carrier substances (lactose or glucose). These substances can irritate the hyperreactive airways of asthmatic patients. The fluorocarbonated propellants pollute the atmosphere by diminishing the ozone layer and by increasing the "greenhouse effect" (7). Further, some patients are unable to use a metered dose inhaler despite adequate instruction, especially children and elderly patients. The most common error is failure to coordinate the inhalation with activation of the spray (5). The BT is a breath-actuated dry powder inhaler designed to overcome this problem. It is based on the principle of using a dry powder of pure terbutaline which breaks down into a fine cloud for inhalation

when agitated in a turbulent airstream: the patient's inspiratory airflow. The inhaler is equipped with a bulk powder supply of 200 doses of drug and dispenses 0.5 mg terbutaline per dose.

The aim of the study was to compare the bronchodilator dose-response and adverse effect of terbutaline when administered with a conventional metered dose inhaler (Bricanyl® MDI) and with a dry powder inhaler (Bricanyl Turbuhaler®).

MATERIAL AND METHODS

Patients

Nine patients were included (4 female, 5 male, 20-46 years of age; mean 30 years). All patients suffered from chronic bronchial asthma with a duration of 2-34 years (mean 16 years). They were all experienced in the daily use of bronchodilating inhalers. The study was of an open, randomized, crossover, cumulative, dose-re-

sponse design. It was carried out on 2 separate days with an interval of 2 to 9 days (mean 6 days). Differences in baseline forced expiratory volume in the first second (FEV_1) $> 15\%$ between the 2 days were not allowed.

Patients suffering from cardiac disease, hyperthyroidism, diabetes and hypersensitivity to sympathomimetics, or in treatment with β -blocking agents, were not considered for study. The patients were out-patients, attending the allergy clinic at Roskilde County Hospital. They were all informed and consent was obtained. The baseline FEV_1 had to be less than 70% of predicted normal value (4). Within 1–2 weeks before the study the patients had to show reversibility of airways obstruction after 2 puffs from a β_2 -agonist spray (0.5 mg terbutaline or 0.2 mg salbutamol) with an FEV_1 improvement of at least 20%. Theophyllines, oral/inhaled β_2 -agonists and anticholinergics, had to be withdrawn within the previous 48, 12/8 and 8 h, respectively. Concomitant steroids and/or antihistamines were continued at a constant level.

Doses of terbutaline were given at 30-min intervals to a maximum cumulative dose of 5 mg. On the MDI test day, the patients inhaled 1, 1, 2, 4, 8 and 4 inhalations (0.25 mg/inhalation). On the BT test day, the patients inhaled 1, 1 (0.25 mg/inhalation) and 1, 2 and 4 inhalations (0.5 mg/inhalation) and after that 4 inhalations from MDI (0.25 mg/inhalation), to ensure that maximum bronchodilation was obtained. The patients' inhalation flow-volume curves were recorded with a hot wire spirometer (Monaghan 403[®]) connected to an oscilloscope, and the patients were instructed to keep the inspiratory flow at approx. 60 l/min. The actuator of the MDI was modified to connect with the spirometer probe to allow measurement of the airflow through the inhaler. The BT was built into a test cover and connected to the spirometer probe for flow measurement. Inhalation flow curves were plotted by a Kipp & Zonen x/y-recorder.

The following parameters were measured: Peak inspiratory flow (PIF) and forced inspiratory volume (FIV₁, FIVC) at each inhalation. FEV_1 , forced vital capacity (FVC) (best of 3 attempts) and heart rate 60 and 5 min before

treatment and 5 and 20 min after each inhaled dose. Measurement by the Vitalograf Spirometer[®]. Muscle tremor 60 and 5 min before treatment and then 25 min after each inhaled dose. Muscle tremor was measured by an optoelectronic tremograph attached to the middle finger, and the signal from the transducer was transformed to a curve and plotted by the x/y recorder. Airway irritation, taste sensation or other adverse effects were recorded at each measurement. The paired Student's test was used for statistical calculation of the data.

RESULTS

The increase in FEV_1 after two doses of a β_2 -agonist spray according to the inclusion criteria was 21–71%, mean 36%. Although the patients were instructed to keep a flow of 60 l/min, during inhalation the mean peak inspiratory flow through the BT was 68 l/min and 181 l/min through the MDI. The mean inhaled volume for BT was 4.7 l, and for MDI 3.9 l. As the degree of bronchodilation was generally higher at 20 min after the given doses than after 5 min, only the 20-min values for FEV_1 , FVC and heart rate are given in Figs. 1–3. Increase in FEV_1 , FVC, heart rate and muscle tremor were plotted against bronchodilating dose. The mean dose-response FEV_1 curves are given in Fig. 1. Both treatments show a statistically significant increase over basal value for all doses ($P < 0.001$). There was no statistically significant difference between the two treatments. The mean dose-response FVC curves are given in Fig. 2. Both treatments show a statistically significant increase over basal value for all doses ($P < 0.001$). There was no statistically significant difference between the two treatments. The mean heart rate dose-response curves are given in Fig. 3. Both treatments showed an increase in heart rate. For the BT it was significant after a cumulated dose of mg: 0.25, 1, 2 and 4 (with P values < 0.05 , 0.01, 0.01 and 0.001 respectively). For MDI it was significant after a cumulated dose of 4 mg ($P < 0.05$). There was no statistically significant difference between the two treatments. The mean tremor

Volume (l)

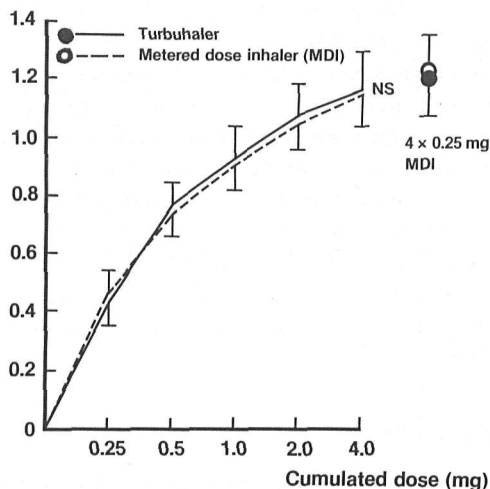


Fig. 1. Increase in FEV₁ over basal value at 20 min after inhalation. (Mean $\pm$ SEM) $\circ$ and $\bullet$ indicates inhalation with 4×0.25 mg from a metered dose inhaler (MDI).

Heart rate (beats/min)

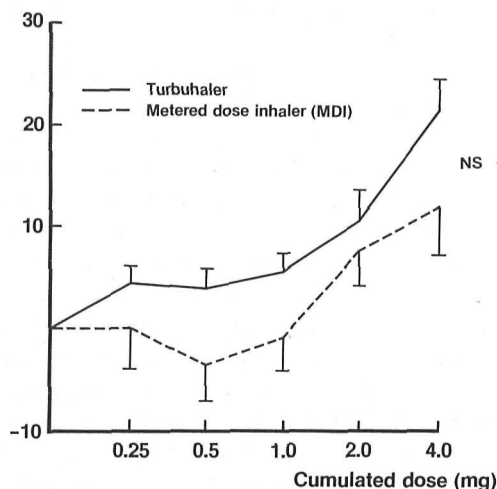


Fig. 3. Increase in heart rate over basal value at 20 min after inhalation. (Mean $\pm$ SEM).

Volume (l)

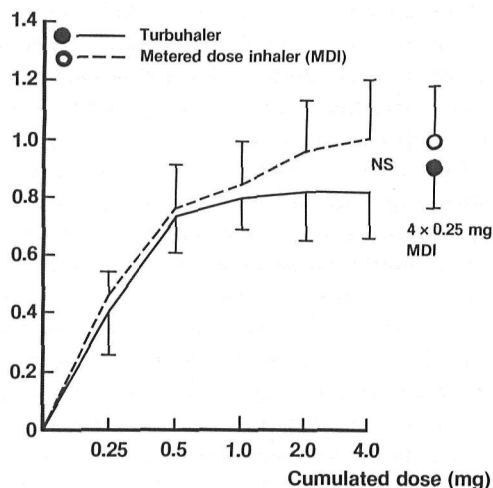


Fig. 2. Increase in FVC over basal value at 20 min after inhalation. (Mean $\pm$ SEM) $\circ$ and $\bullet$ indicates inhalation with 4×0.25 mg from a metered dose inhaler (MDI).

Tremor (mm/10s)

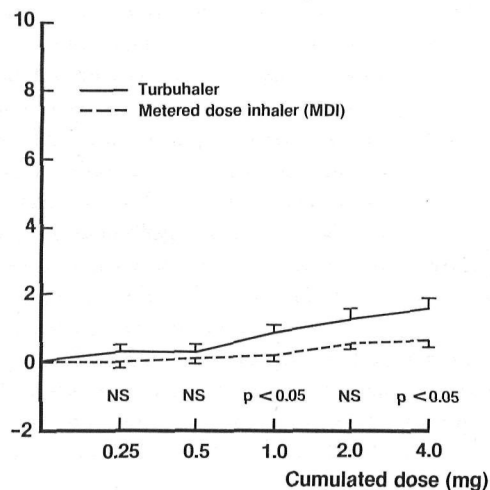


Fig. 4. Increase in tremor over basal value at 25 min after inhalation. (Mean $\pm$ SEM).

dose-response curves are given in Fig. 4. After a cumulated dose of 1 mg, tremor was significantly persistent for both treatments ($P <$

0.01). There was a significant difference between the two treatments after a cumulated dose of 1 and 4 mg ($P < 0.05$). The values of the curves were taken 25 min after inhalation.

Bitter, sweet, powder, or rubber taste sensa-

tions were recorded. Nine patients noted this on BT day and 6 on MDI day.

DISCUSSION

Our data revealed no difference in bronchodilating dose-response effect (FEV_1 and FVC) between the BT and the MDI. There was a more marked increase in heart rate and muscle tremor when the BT was used, perhaps because of a greater systemic absorption. Both side effects are well known for terbutaline (3, 9). No serious adverse effects were noticed. The inhalation flow curves showed a more even flow when BT was used; and, due to the greater inspiratory resistance in BT, inspiratory flow was only 68 l/min. It has been pointed out by Newman (8) that bronchodilation response to terbutaline sulphate is better at low flow rates. This speaks in favour of BT.

Conclusion

BT treatment is as effective as MDI treatment when equal doses of terbutaline are given. It is easy to apply and the failure, with the MDI, to coordinate inhaler actuation with inspiration is avoided. BT contains no chlorofluorocarbonated propellants or additives and it is therefore possible to avoid the irritating effects that some patients may experience from these substances in MDI's.

ACKNOWLEDGEMENTS

We wish to thank the nurses at the Allergy Clinic, Roskilde County Hospital, for their skilful help during the study, and the Draco Respiratory Group for placing Turbuhalers® and MDIs at our disposal.

REFERENCES

1. Arner, B., Bertler, Å., Karlefors, T. & Westling, H.: Bronchodilator effect of a new sympathomimetic β -receptor-stimulating agent, terbutaline, given to asthmatic patients. *Acta Med. Scand. Suppl.* 512: 41-43, 1970.
2. Bateman, J. R. M., Pavia, D., Sheahan, N. F., Newman, S. & Clarke, S. W.: Effects of terbutaline sulphate aerosol on bronchodilator response and lung mucociliary clearance in patients with mild stable asthma. *Br. J. Clin. Pharmacol.* 15, 695-700, 1983.
3. Bowman, W. C.: Effects of adrenergic activators and inhibitors on the skeletal muscle. In Szekeres, (ed.): *Adrenergic activators and inhibitors. Handbook of experimental pharmacology*, pp. 47-128. Springer Verlag, Berlin, 1981.
4. Cotes, J. E.: Lung function. Assessment and application in medicine, pp. 316-356. 4th ed. Oxford, Blackwell, 1979.
5. Crompton, G. K.: Problems patients have using pressurized aerosol inhalers. *Eur. J. Respir. Dis.* 63 Suppl. 119, 101-104, 1982.
6. Editorial: Fluorocarbon aerosol propellants. *Lancet* 1, 1073-1074, 1975.
7. Maugh, T. H.: What is the risk from chlorofluorocarbons? *Science* 1984: 223, 1051-1052, 1984.
8. Newman, S. P.: Deposition and effects of inhalation aerosols pp. 80-84. Lund, Sweden, Rahm, 1983.
9. Sackner, M. A., Dougherty, R., Watson, H. & Wanner, A.: Haemodynamic effects of epinephrine and terbutaline in normal man. *Chest* 68, 616-624, 1975.

Address:

Claus Richard Johnsen, M.D.
Clinic of Allergy
Roskilde Amts Sygehus
Køgevej 9-13
DK-4000 Roskilde
Denmark

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.