

A New Inhalation Technique for Freon Aerosols

Terbutaline Aerosol with a Tube Extension in a 2-Day Cross-Over Comparison with Salbutamol Aerosol

N. E. ERIKSSON, K. HAGLIND and K. G. HIDINGER

Dept. of Medicine, Länssjukhuset, Halmstad and AB Draco*, Medical Department, Lund, Sweden

In a double-blind, cross-over, 2-day study 32 adult asthmatic patients compared the bronchodilating effect of 0.5 mg terbutaline sulphate aerosol, administered via a 10 cm tube extension attached to the actuator of a pressurized aerosol, with that of 0.2 mg salbutamol sulphate, administered by a conventional pressurized aerosol. New instructions for the inhalation technique were given for the terbutaline aerosol, dividing the actuation of the aerosol and the slow inhalation into two steps. The salbutamol aerosol was to be taken according to the instructions enclosed, i.e. coordinating the actuation of the aerosol and the inhalation.

The improvement in peak expiratory flow rate (PEFR) values was similar for the two treatments. Subjective assessments by the patients showed no differences between the two regimens.

As the effect seems to be equal, an aerosol actuator furnished with a tube extension, with no strict demands of synchronizing the actuation of the aerosol and the inhalation, could be a suitable alternative treatment in patients who find self-administration with conventional asthma aerosols difficult.

Key words: asthma therapy; beta-adrenergic receptor agonists; pressurized aerosols; salbutamol; terbutaline

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β_2 -stimulators are an effective means of treating bronchial asthma. Local administration by an aerosol reduces those side-effects, especially tremor, that can be seen after oral ingestion of β_2 -stimulators (6).

Some patients, however, still experience side-effects with aerosol treatment. This is probably due to the fact that a great deal of the dosage administered is impacted in the oral cavity and pharynx, and is subsequently swallowed and absorbed from the gastrointestinal tract (10). Another problem connected with the pressurized aerosols is that many patients have difficulties in coordinating the actuation of the aerosol and the inhalation (3, 11). As the therapeutic effect of a

conventional aerosol is reduced when the actuation and the inhalation are not synchronized (1), a technical device that does not demand such synchronization would make a more efficient therapy possible.

Airway-related factors, such as flow rate, tidal volume and airway calibre, as well as particle-related factors, such as size, shape, and density, determine the sites of aerosol deposition in the lung (9). A study in healthy volunteers has shown that the deposition of drug substance in the oral cavity can be reduced if a tube extension is attached to the aerosol actuator (8). When delaying the inhalation 5 sec after actuating the aerosol, the total loss of terbutaline sulphate in the actuator, the tube, and the oral cavity was not

*Subsidiary of AB Astra, Sweden

significantly greater than when the ordinary actuator was used according to the instructions given so far.

It has previously been shown that the inhalation of 0.25 mg terbutaline sulphate gives the same clinical effects as 0.1 mg salbutamol sulphate (4). The aim of the present study was to investigate if this equipotency still remained when terbutaline sulphate (Bricanyl[®], Draco) was furnished with a tube extension, using a new inhalation technique with the actuation of the aerosol and the inhalation divided in two different steps. The salbutamol sulphate aerosol (Ventolin[®], Glaxo) was used according to the instructions enclosed in the package.

PATIENTS AND METHODS

Thirty-six adult asthmatic patients, well known to the clinic, having a reversibility of their airways obstruction of at least 15%, were selected for the study. Four of the patients could not fulfill the study. The remaining 32 patients, 11 men and 21 women, had a mean age of 44 years (range 19–69). Their pre-treatment morning PEFR value was 60% (range 26–110%) of their predicted value. Four of the patients were smokers (3–15 cigarettes/day). Before the study all patients were on β_2 -stimulants (aerosol and/or tablets) and 17 were on theophyllines. These drugs were withdrawn at least 8 h prior to the start of the study. Cough remedies as well as nasal decongestants were allowed as prescribed by the physician. Other concomitant medication connected with the patients' airways disease during the trial was beclomethasone dipropionate aerosol in 24 patients and oral corticoids in nine patients.

The study was designed as a double-blind, 2-day cross-over procedure using a double-dummy technique with self-recording of PEFR at home by the patients as described by Lal et al. (5). All patients were randomly allocated into two treatment groups. One group received a box containing a terbutaline sulphate aerosol, giving 0.25 mg per actuation, supplied with a tube extension

32 × 36 × 100 mm and a salbutamol sulphate placebo aerosol for the first day. For the second day of the experiment, the patients received another box containing one salbutamol sulphate aerosol giving 0.1 mg per actuation and one terbutaline sulphate placebo aerosol

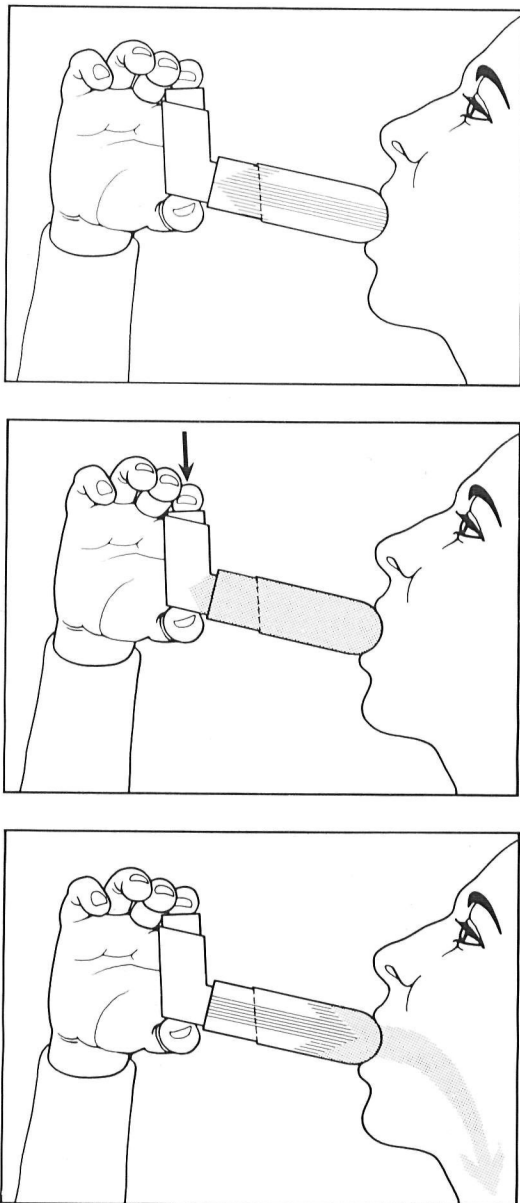


Fig. 1. The new inhalation technique. From the top: exhale, actuate, inhale.

supplied with a tube extension. The other treatment group received the aerosols in the reversed order.

The salbutamol aerosol was used according to the instructions enclosed in the commercially available package, i.e. the dose was to be administered at the beginning of a deep inhalation. The terbutaline aerosol with the tube extension was used according to the new instructions illustrated in Fig. 1.

At a meeting all details of the trial were carefully explained to the patients. Each patient received a mini-Wright peak flow meter (13), two boxes with aerosols marked Day 1 and Day 2 respectively, and protocols for registering PEFR, side-effects and concomitant medication. The patients were asked to carry out the trial during 2 consecutive days within the next fortnight and then return the protocols by mail.

On each of the days in the study PEFR was registered twice in the morning, 10 min apart, before any medication was taken. Then two puffs were taken with a 30-sec interval from each of the two aerosols in the box marked with the appropriate day. PEFR was registered 5 min, 30 min, and hourly after taking the aerosols. On each occasion three attempts were made to measure PEFR.

The patients were told to stop registering PEFR when any of the following circumstances occurred: 1) PEFR returned to pre-drug level, or 2) the need to inhale from an openly labelled bronchodilator aerosol was strong, or 3) 10 p.m. arrived. After completing

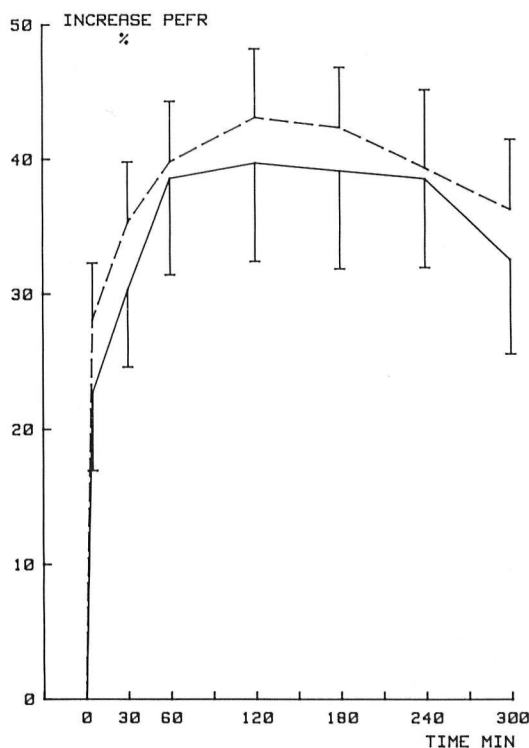


Fig. 2. Percentage increase in PEFR. Mean $\pm$ s.e.m. in 24 patients with a duration of action of at least 5 h on both days. — 0.5 mg terbutaline aerosol with tube extension; - - - 0.2 mg salbutamol aerosol.

the registration of PEFR the patients took their ordinary bronchodilating drugs.

At the end of the 2nd day the patients stated whether they felt much better, better, the same, worse, or much worse compared with the first day of the experiment. The patients'

Table 1

Initial and maximum PEFR values in 32 asthmatic patients after inhalation of 0.5 mg terbutaline sulphate aerosol with tube extension and 0.2 mg salbutamol sulphate aerosol

	Initial PEFR value (l/min)		Maximal PEFR value after aerosol (l/min)		Level of significance
	$\bar{x}$	S.E.M.	$\bar{x}$	S.E.M.	
Terbutaline aerosol with tube extension	314	22	431	20	$P < 0.001$
Salbutamol aerosol	301	21	428	21	$P < 0.001$

Table 2

Terbutaline with tube extension compared to salbutamol

	Much better	Better	Same	Worse	Much worse	Missing data
According to subjective assessment of symptoms	1	4	14	9	2	2
According to calculations from AUC	4	7	11	7	3	0

statements were compared with the calculated area under curve (AUC). Deviations of less than 10% between the 2 days were considered 'the same'; deviations of 10–50% were considered 'better or worse'; and a deviation of more than 50% was considered 'much better or much worse'.

All PEFR-recordings used in the statistical calculations were the best of three attempts. Student's paired t-test was carried out on the maximum increase and on the longest duration of action of the aerosols, as well as on AUC. Comparisons between the drugs regarding subjective assessments as well as assessments according to calculated AUC were made with an χ^2 -test with Yate's correction.

RESULTS

Four patients of the totally 36 who entered the study never completed it. One patient did not understand the instructions given, a second experienced a deterioration of the asthma, and another two patients suffered from other diseases during the fortnight when the trial was to be carried out.

The initial PEFR values on the 2 days of the study did not differ significantly, nor was there any significant difference between the two pre-treatment PEFR values recorded with a 10-minute interval. There was a highly significant ($P < 0.001$) increase in PEFR (Table 1 and Fig. 2) after inhalation of each of the two drugs, but no significant difference between the two drugs in maximum increase of PEFR.

The duration of action was similar for the two drugs. Terbutaline sulphate aerosol with the tube extension gave a longer duration in 13 patients. Salbutamol aerosol gave a longer duration in 14 patients. In five patients the effect was equally long for both drugs.

The AUC was 2514 ± 274 l (mean $\pm$ s.e.m.) for the terbutaline sulphate with the tube extension and 2550 ± 255 l for the salbutamol sulphate. There was no significant difference between the two drugs.

The patients' subjective assessment of their symptoms on Day 2 compared to Day 1, as well as assessments calculated from AUC, are seen in Table 2. A good concordance was seen to prevail when the subjective statements were compared with the assessments calculated. There was no significant difference between the two drugs tested.

Side-effects were noted by three patients. One patient noted a slight local irritation in the throat on both days. A second patient had cough and a slight irritation in the throat, and a third patient experienced tremor, lasting for 30 min after taking salbutamol sulphate aerosol.

DISCUSSION

The efficacy of topical treatment with inhaled bronchodilators depends on the proportion of the inhaled substances deposited in the lung. Only about 10% of the dose inhaled from a

conventional aerosol enter the airways (2). This proportion can be influenced by the degree of obstruction and the inhalation technique as well as by the characteristics of the particles (9, 12). As the use of a tube connected with the actuator of a pressurized aerosol decreases the impaction of drug in the apparatus and in the mouth (8), one could expect a better bronchodilating effect with such a modified actuator compared with a conventional one.

Lindgren et al. (7) have, in an open trial, studied the short-time effect of three doses of terbutaline sulphate aerosol, administered via an ordinary pressurized aerosol as well as combined with two different spacers, a pear-shaped one and a straight one of the same type as the one we used in our study. They found that inhalation via the pear-shaped spacer produced a significantly better bronchodilating effect than the actuator alone, whereas the straight tube gave only a slight, if any, improvement, compared with the standard actuator. Studying the effect of 0.5 mg terbutaline sulphate with standard aerosol as well as with a 10-cm tube spacer, Bloomfield et al. (1) did not record any significant difference between the two types of inhalation when the actuation and the inhalation were coordinated. When using the conventional aerosol the bronchodilating effect was significantly poorer when the inhalation was unsynchronized with the actuation. On the other hand, the spacer, when used in an unsynchronized manner, gave results comparable to the conventional aerosol used synchronized. They concluded that the tube spacer, at least partly, could compensate for poor coordination.

In the present study, the effect of the therapy measured by PEFr at home was compared—after the administration of terbutaline sulphate aerosol with a tube extension—with that of a standard salbutamol sulphate aerosol. No significant difference was found between the two modes of inhalation. The patients taking part in the study were cooperative. They had been in contact with

the clinic for several years and thereby received thorough instructions on how to use the metered aerosol. There is reason to believe that all participants were able to use a conventional metered aerosol correctly, i.e. pressing the actuator at the beginning of the inhalation. As one of the advantages of the modified aerosol is that an effective inhalation is simplified for patients having difficulties with this coordination, it would probably be worth while to carry out a similar study in patients having difficulties in using conventional metered aerosols correctly.

One advantage gained from the tube extension is that less drug is deposited in the oral cavity (8). As the deposited drug will be swallowed (10) it could be expected that when a tube extension is attached, less side-effects should occur. In this study, only a few patients experienced side-effects. Only an investigation using higher doses of β_2 -stimulants could answer the question whether any difference in side-effects will occur with the two methods.

To summarize: In this study, the effects of a terbutaline sulphate aerosol with a tube extension without demands for coordination, was shown to be equal with the effects of a conventional salbutamol sulphate aerosol. A pressurized aerosol with a tube extension must be considered a simplification of the inhalation technique. Patients having difficulties in synchronizing the actuation of the aerosol and the inhalation should derive benefit from the modified aerosol inhalers.

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Address:

Dr. N. E. Eriksson

Department of Medicine

Länssjukhuset

S-301 85 Halmstad

Sweden

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