Simple instructions for using pressurized aerosol bronchodilators[1]

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Summary: Although the manufacturers of pressurized aerosol bonchodilators issue instructions for using the inhalers, little or no experimental verification exists. Bronchodilatation has been measured after controlled inhalations of 500 μg terbutaline sulphate given in a systematic series of investigations to 8 patients with reversible airways obstruction at 2 different inhalation flow rates (25 l/min and 80 l/min), 3 different lung volumes (20%, 50% and 80% vital capacity) and followed by 2 different breath-holding pauses (4 and 10 seconds). The results indicate that patients may release the aerosol at any time during the course of a slow deep inhalation which should be followed by 10 seconds of breath-holding. This will ensure an optimal bronchodilator response.

Introduction

In the treatment of asthma, inhalation of therapeutic aerosols is often preferred to other routes of administration since it offers a rapid onset of action (Plit *et al.* 1972) and a low incidence of side effects (Sterling 1978). Pressurized metered dose inhalers (MDIs) are the most socially acceptable method for aerosol delivery, and inhalers containing beta-adrenergic, anticholinergic and steroid drugs are commercially available. The manufacturers of pressurized aerosols issue a set of instructions to patients for their use, and recommended techniques of inhalation have also been published in a number of review articles (Miller 1973, Butler 1973, Grainger 1977). A typical set of instructions is shown in Table 1. Patients are

Table 1. Typical instructions for using pressurized aerosol metered dose inhalers

Inhaled volume:	Inhale from residual volume to total lung capacity
Inhaled flow rate:	Usually unspecified, but 'sudden' or 'quick' inhalation may be recommended
Lung volume of aerosol release:	Usually unspecified
Breath-holding	'For a few seconds' or 'for as long as possible'
Repeat dose:	Either immediately or five minutes later

usually advised to take a deep inhalation, but apart from this there are wide variations in the instructions, particularly with regard to the speed of inhalation and to the duration of the subsequent breath-holding period. These uncertainties are confusing to both patients and doctors, and it is not surprising that a high proportion of asthmatics use their inhalers inefficiently (Orehek *et al.* 1976, Paterson & Crompton 1976, Earis & Bernstein 1978).

In preliminary studies (Newman *et al.* 1979*a*), after inhaling 2 puffs (500 μg) terbutaline sulphate from an MDI during slow (25 l/min) full inspirations, 10 seconds breath-holding produced maximal bronchodilatation, whereas 4 seconds gave significantly less. In the present study the effects of speed of inhalation, time of activation of the MDI (Riley *et al.* 1976, Riley *et al.* 1979, Newman *et al.* 1979*b*) and breath-holding pause on bronchodilatation have been

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examined further. The aim was to identify the correct method for using an inhaler, which in turn would lead to better bronchodilatation and patient compliance.

Methods

To control inhalation an MDI was joined to a heated pneumotachygraph and sealed so that air could be drawn only through the pneumotachygraph (Figure 1). Variable fine holes in the inlet port enabled slow or fast inhalations to be performed. The differential pressure signal from the pneumotachygraph was fed to a respiratory flow integrator (P K Morgan Ltd), and inhaled volume was subsequently displayed continuously on an ultraviolet recorder (SE Laboratories).

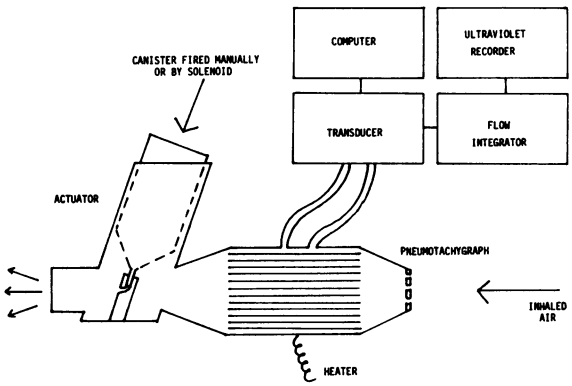

Figure 1. Inhalation apparatus used to perform controlled inhalations of a pressurized aerosol. Inhaled flow rate was recorded by a pneumotachygraph placed in series with the aerosol actuator and was restricted by the size of fine holes in the opposite end of the pneumotachygraph. The differential pressure signal was fed to a transducer and was then integrated to give inhaled volume, and the aerosol canister was fired either manually or by a computer operated solenoid

Each subject first performed several trial inhalations in order to measure the vital capacity (VC). In the slow flow rate studies, 2 puffs (500 μg) of terbutaline sulphate (Bricanyl, Astra Pharmaceuticals) were then released manually from a pressurized canister during vital capacity inhalations at a known lung volume by observation of the ultraviolet recorder trace. The first and second puffs were separated by approximately 30 seconds. Fast flow inhalations of 2 puffs (500 μg) terbutaline sulphate were carried out with the pneumotachygraph signal fed to a Varian V 77 200 computer, which carried out the integration of the flow rate signal (Newman *et al.* 1980). During the course of inhalation, the aerosol canister was then fired by a solenoid mounted on top of the aerosol actuator at a lung volume which could be preset by means of a computer program written in Fortran.

Eight patients with reversible airways obstruction (6 asthmatics, 2 chronic bronchitics, mean baseline forced expiratory volume in one second (FEV_1) 49% predicted, mean reversibility >20%) each performed a total of 9 randomized studies involving controlled inhalations of 500 μg terbutaline sulphate. Consecutive studies were separated by at least one day. Three studies involved a slow inhaled flow rate and the remaining 6 studies a fast inhaled flow rate. The details of the studies were as follows: slow flow rate, 10-second breath-holding – dose given at 20%, 50% or 80% VC; fast flow rate, 10-second breath-holding – dose given at 20%, 50% or 80% VC; fast flow rate, 4-second breath-holding – dose given at 20%, 50% or 80% VC. Bronchodilator response was assessed by measuring FEV_1 using a Vitalograph spirometer immediately before inhalation and then 5, 15, 30, 60, 90 and 120 minutes later.

All patients gave their informed consent, and the studies were approved by the Ethical Practices Committee of the hospital. Oral and inhaled bronchodilators were withheld for 12

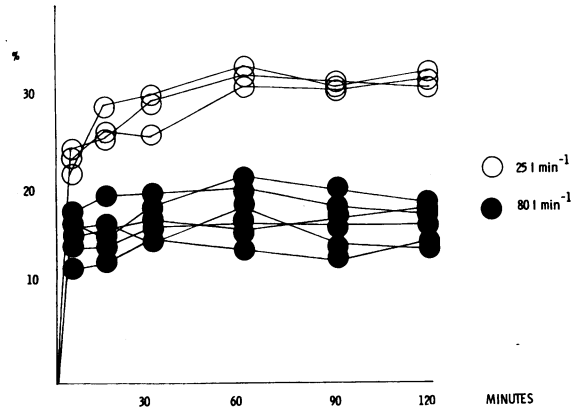

Figure 2. Percentage increases in FEV_1 are plotted against time following controlled inhalations of 500 μg terbutaline at 25 l/min or 80 l/min. Each patient performed 3 studies at 25 l/min and 6 studies at 80 l/min involving various lung volumes and breath-holding pauses.

hours prior to the commencement of each study, but patients maintained on steroid therapy continued to take their usual dose. Wilcoxon rank sum tests, both for paired and unpaired data, and analysis of variance were used to assess statistical significance.

Results

The increases in FEV_1 are shown in Figure 2. Changes in FEV_1 15 minutes after inhalation (Table 2) were greatest with the slow flow rate and were significantly ($P<0.05$) reduced with the fast flow rate, for studies carried out with both 4 and 10 seconds of breath-holding. There were no significant differences between the levels of bronchodilatation achieved in any of the fast flow rate inhalation studies. This pattern of bronchodilator response was also found when changes in FEV_1 were analysed at other time intervals up to 2 hours. Baseline FEV_1 values were not significantly different on any study day, whether expressed in absolute terms or as percentages of predicted values.

Table 2. Percentage changes (mean ± s.d.) in FEV_1 15 minutes after inhaling 500 μg terbutaline sulphate

Inhaled flow rate	Breath-holding pause (seconds)	Lung volume of aerosol release		
		20% VC	50% VC	80% VC
Slow	10	29.5 ± 14.3	27.0 ± 19.2	26.7 ± 13.2
Fast	10	16.6 ± 11.6	14.2 ± 9.7	12.7 ± 8.6
Fast	4	20.1 ± 16.2	15.2 ± 8.6	16.5 ± 11.9

Discussion

Our results show that maximal bronchodilatation, as indicated by percentage increase in FEV_1, is achieved with a slow, full breath and 10 seconds of breath-holding, the lung volume at which the aerosol is inhaled being unimportant. With rapid inhalation, bronchodilatation was significantly reduced irrespective of the breath-holding pause or the lung volume of aerosol inhalation. This may occur because the majority of aerosol particles entering the lungs during rapid inhalations are deposited in large central airways by inertial impaction (Goldberg & Lourenco 1973) and only a small number are able to penetrate to more peripheral regions, where beta-adrenergic bronchodilators are believed to have their site of

action (Hensley *et al.* 1978). The figures in Table 2 may be compared with the results of our previous study (Newman *et al.* 1979*a*) in which increases in FEV_1 with slow inhalation and 4 second breath-holding were $14.4 \pm 10.9\%$, $9.6 \pm 5.5\%$ and $8.0 \pm 5.5\%$ for inhalations at 20%, 50% and 80% VC, respectively. Two factors stand out overall: firstly, the slow inhalation flow rate and, secondly, the 10-second breath-holding pause, both of which appear to be required for optimal bronchodilatation.

Patients can be given the following simple instructions for obtaining maximum benefit from their pressurized bronchodilators. They should be advised to shake the canister thoroughly; place the inhaler mouthpiece between the lips; breathe out steadily; fire the inhaler while taking a slow, deep inhalation; and hold the breath at full inspiration while slowly counting to 10.

Our findings are in contrast to the instructions issued with several inhalers, which recommend taking a full breath but at the same time inhaling 'quickly' or 'suddenly'. Such instructions are hard to reconcile with the facts known about aerosol deposition, as a fast flow rate causes aerosol to deposit in central airways and a deep inhalation produces a more peripheral distribution of aerosol (Pavia *et al.* 1977). The fast inhalation flow rate used in this study (80 l/min) is typical of that normally attained by patients when using their inhalers (Coady *et al.* 1976), and substantial re-education would be required to ensure a slow inhalation flow rate. The manufacturers of the pressurized aerosols could assist in this by reducing the width of the annulus between actuator and canister so that air could only be drawn through at a slow rate.

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