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The output of flunisolide from different nebulisers

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Abstract

The objective of this study was to determine the output, in-vitro, solution of a concentrated solution of flunisolide from two different nebulisers under simulated breathing conditions. The BimboNeb and Nebula nebulisers were used to nebulise 2.6 mL of flunisolide solution (600 μg). Particle size was determined by inertial impaction and the total output of drug from the nebulisers under simulated breathing conditions was measured using a sinus flow pump. Two different breathing patterns were used, simulating nebuliser use by a child and an adult. The mass median aerodynamic diameter of flunisolide particles from the BimboNeb and Nebula were both 3.9 μm. With the simulated paediatric breathing pattern, both nebulisers delivered similar amounts of flunisolide (56.4 μg (s.d. 1.4 μg) and 56.1 μg (5 μg) over 5 min from the BimboNeb and Nebula, respectively). With the adult breathing pattern, flunisolide delivery from the BimboNeb was increased to 88.9 μg (3.3 μg), but delivery from the Nebula was only slightly increased to 64.6 μg (1.4 μg). With both nebulisers, little drug was released after 5 min of nebulisation. Both nebulisers delivered 9–15% of the nominal dose of flunisolide to the breathing simulator, a similar percentage to previous studies with budesonide and more than previous studies with beclometasone. Drug delivery from the BimboNeb, but not the Nebula, was affected by the simulated breathing pattern. This study suggests that drug delivery from nebulisers is dependent upon the interaction between the nebuliser, the drug and the patient.

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Introduction

Corticosteroid therapy by nebuliser is commonly prescribed to patients with asthma and chronic obstructive airways disease. The majority of corticosteroid preparations available for nebulisation are formulated as suspensions. When nebulised, the corticosteroid particle is surrounded by an envelope of carrier fluid, and many of these aerosolised particles will be too large to enter the respiratory tract (O'Callaghan 1990). This is thought to be the reason for the disappointing clinical performance of some nebulised corticosteroids (Storr et al 1986; Webb et al 1986). Flunisolide is available for nebulisation in a solution form. It is likely that more drug will be nebulised in smaller particles from a solution, although this will depend on the nebuliser and compressor used (O'Callaghan & Barry 1997).

Patient factors may also affect drug delivery from nebulisers. Nebuliser output is fixed by the driving gas flow and the resistance of the nebuliser, and is constant throughout drug delivery. A patient's inspiratory flow, by contrast, will vary according to the respiratory pattern. Entrainment occurs when the patient's inspiratory flow rate exceeds the nebuiliser output. Only the youngest patients have inspiratory flows lower than commonly used nebuliser outputs; for the others, the aerosol will be diluted by entrained air (Collis et al 1990). Previous studies suggest

that patient respiratory pattern may affect drug delivery from nebulisers (Barry & O'Callaghan 1998).

There is no information on the likely effect of different patient breathing patterns on the delivery of flunisolide from different nebulisers. Physicians and patients need well-defined information about their inhalational drug delivery device to optimise therapy (O'Callaghan & Barry 1999).

The aim of our study was to estimate the amount of drug contained in particles likely to reach the lungs and the total amount of flunisolide solution that would be inhaled by children and adults from two commonly used nebulisers.

Methods

Nebulisers and medication

The nebulisers and compressors used were the Bimbo-Neb (Mefar, Bovezzo (BS) Italy) and the Nebula (Markos, Monza (MI) Italy). Flunisolide solution was made by accurately adding 0.6 mL (600 μg) of flunisolide (Lunibron A, Valeas s.p.a. Pharmaceuticals, Milan, Italy) to 2 mL of 0.9% saline for each experiment.

Particle size measurements

The experimental methods have been previously described in detail (O'Callaghan et al 2000). The particle size distribution of the aerosol clouds produced during nebulisation was measured using a glass multistage liquid impinger (MSLI; Bell et al 1973). The nebulisers were charged with 2.6 mL of flunisolide solution (600 μg) and the nebuliser mouthpiece held against the throat of the MSLI. The aerosol cloud was lit by back illumination to ensure that it was drawn into the impinger.

After each experiment the nebulisers and experimental apparatus were washed with solvent and the amount of drug collected in each part assayed by high-pressure liquid chromatography (HPLC). Each nebuliser was tested 4 times.

Breathing simulation

Total drug output from the nebulisers was measured using a breathing simulator (Pari Sinus Breathing Simulator, Pari GmbH, Starnberg, Germany) which allows simulated tidal volume, respiratory rate and inspiratory time to be independently adjusted. Flunisolide solution (2.6 mL, 600 μg) was added to the nebuliser, which was attached to the breathing simulator. Electrostatic filter pads were used to collect the aerosolised drug, held in a plastic filter assembly (dead space 11 mL). The mouthpiece supplied by the nebuliser manufacturer connected nebulisers to the filter assembly. Waste aerosol released during expiration was collected on an expiratory filter. The experimental apparatus is shown schematically in Figure 1. The nebuliser was operated for 5 min. Nebulisation was stopped after 5 min and both filters were changed. Nebulisation was continued for a further 5 min (total 10 min) and then stopped. Filters were removed from the housing and the amount of flunisolide deposited on them determined by HPLC.

Two different breathing patterns were used, one to represent a child's breathing pattern, and one to represent an adult breathing pattern. The tidal volume, respiratory rate and inspiratory fraction were 150 mL, 20 breaths per minute and 40% and 600 mL, 12 breaths per minute and 40%, respectively. These settings gave a minute volume, maximum inspiratory flow and mean inspiratory flow of 3 L min^{-1}, 11.8 L min^{-1} and 7.5 L min^{-1} and 7.2 L min^{-1}, 28.3 L min^{-1} and 18 L min^{-1} for the two breathing patterns, respectively. Each

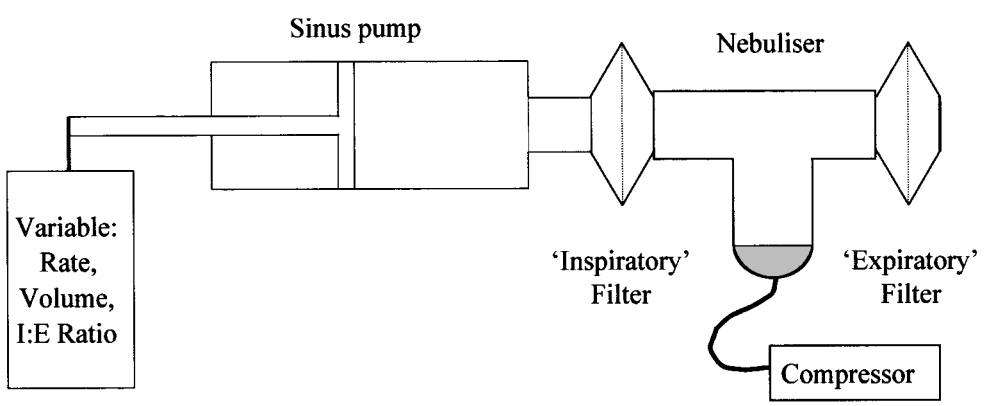

Figure 1 Schematic representation of the breathing simulator experimental apparatus.

nebuliser was assessed at each breathing pattern on four occasions.

Flunisolide assay

The amount of flunisolide present in each of the experimental samples was determined in triplicate by HPLC with UV detection at 254 nm. Chromatograms were integrated using Summit software (Comus, Middlesborough, UK). Calibration checks were made by multiple injections of standard solutions before and after each experimental run. The variation of standard injections was less than 3%.

Statistical methods

Size distribution of the aerosol cloud was determined from the drug recovered from each stage, the MSLI having previously been calibrated with an aerosol of known particle size distribution. From this a log probability plot was constructed, the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were determined. The output of flunisolide from the different nebulisers and different breathing patterns was compared using *t*-tests. Statistical significance was assumed at $P < 0.05$.

Results

There was no significant difference in particle size of flunisolide from the two nebulisers ($P > 0.05$), or in total output to the MSLI ($P > 0.05$). However, there were significant differences in the output of the BimboNeb with the different breathing patterns that were not seen with the Nebula.

The MMAD and GSD calculated for the aerosol cloud of flunisolide from the BimboNeb and Nebula are given in Table 1. Using the breathing simulator, the total amount of drug delivered to the filter after 5 min with the paediatric breathing pattern, representing the total drug that would have been delivered to the patient, was 56.4 μg (s.d. 1.4) from the BimboNeb and 56.1 μg (5.0) from the Nebula (Table 2). Extrapolating from the particle sizing experiment, 34 μg (BimboNeb) and 33.5 μg (Nebula) would have been in particles < 4.3 μm. Using the adult breathing pattern increased the drug output from the BimboNeb significantly ($P < 0.01$) to 88.9 μg (3.3), but only slightly increased that from the Nebula to 64.6 μg. Increasing the nebulisation time to 10 min only slightly increased the output of both nebulisers.

Discussion

The use of inhaled corticosteroid therapy is considered by many to be the first line prophylactic therapy in asthma. Nebulisers may be used for drug delivery to patients who require high doses or who are unable to utilise other delivery methods, such as a metered-dose inhaler and spacer (O'Callaghan & Barry 1997). Nebulised flunisolide has been shown to improve symptom scores in infants and young children with recurrent wheezing (de Benedictis et al 1996; Konig et al 1996;

Table 1 Particle sizing data for flunisolide from BimboNeb and Nebula nebulisers.

	BimboNeb	Nebula
MMAD (μg)	3.90 (0.14)	3.90 (0.21)
GSD	1.80 (0.10)	1.90 (0.04)
Total weight (μg) in cloud	246.9 (12.4)	257.7 (16.3)
Amount of flunisolide (μg) contained in particles < 4.3 μm	148.5 (7.4)	154.2 (10.9)
% of Nominal dose	25.00 (1.24)	26.00 (1.81)
% of Total amount of drug leaving nebuliser in particles < 4.3 μm	60.00 (3.01)	60.00 (4.21)
Amount of flunisolide (μg) contained in particles < 6.8 μm	201.0 (10.4)	208.7 (14.4)
% of Nominal dose	33.00 (1.74)	35.00 (2.40)
% of Total amount of drug leaving nebuliser in particles < 6.8 μm	81.00 (4.21)	81.00 (5.59)

MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; s.d. is given in parentheses.

Table 2 Breath simulator analysis of the output of flunisolide from BimboNeb and Nebula nebulisers – paediatric and adult breathing patterns.

	BimboNeb		Nebula	
	Paediatric	Adult	Paediatric	Adult
Total drug (μg) delivered to the filter after 5 min nebulisation	56.4 (1.4)	88.9 (3.3)	56.1 (5.0)	64.6 (1.4)
% of Nominal dose	9.40 (0.23)	14.80 (0.54)	9.40 (0.82)	10.80 (0.23)
Amount of flunisolide (μg) contained in particles < 4.3 μm	34.00 (0.84)	53.50 (1.95)	33.50 (2.97)	38.70 (0.84)
Amount of flunisolide (μg) contained in particles < 6.8 μg	45.90 (1.14)	72.30 (2.64)	45.40 (4.02)	52.30 (1.14)
Total drug (μg) delivered to the filter after 10 min nebulisation	61.50 (1.18)	98.50 (1.13)	59.90 (5.10)	69.30 (2.20)

s.d. is given in parentheses.

Allen et al 1997). The nebulisation of corticosteroid suspensions may be inefficient, and little drug may be released in particles small enough to enter the lung (O'Callaghan 1990), leading to treatment failure (Storr et al 1986; Webb et al 1986). For this reason, a corticosteroid solution may be preferred for nebulisation. In this study, approximately 25% of the nominal dose was emitted from the nebulisers in small particles (< 4.3 μm MMAD) under constant flow conditions, compared with less than 12% of beclometasone, a suspension, in a previous study with these nebulisers (O'Callaghan et al 2000). This compares with 31% of the nominal dose delivered from the metered-dose inhaler and Volumatic spacer in particles smaller than 5 μm (O'Callaghan 1990).

Choice of a reasonable dosage of flunisolide for study purposes was made more difficult by issues surrounding drug delivery. Actual pulmonary deposition of inhaled medications is affected not only by the delivery device, but also by variables unique to the individual. The dose of nebulised medication that actually reaches the lungs and airways is affected by nebuliser fill volume, flow rate, and type (Hardy et al 1993; Hess et al 1996), distance of the nebuliser from the face (Everard et al 1992), breathing pattern (Barry & O'Callaghan 1999), and whether nasal or mouth breathing is used (Everard et al 1993). The degree of acute bronchospasm may also influence drug delivery to the airways (Pedersen 1996).

The two nebulisers delivered similar amounts of flunisolide at the paediatric breathing pattern. Use of the adult breathing pattern, in contrast, increased drug output from the BimboNeb, but had no effect on the output from the Nebula. This may be due to differences in the nebuliser design, with increased flow through the BimboNeb drawing more aerosol from the nebuliser. Only the youngest children have inspiratory flows lower than commonly used nebuliser outputs, and for older children the aerosol will be diluted by entrained air if nebuliser output remains constant (Collis et al 1990). Thus the mass of drug inhaled with each breath from the Nebula would remain constant throughout most of childhood, despite the fact that the body mass may increase five fold. Some centres recommend increasing the concentration of drug placed in the nebuliser with age to account for this.

It is likely, therefore, that a young infant using the Nebula would inhale a much larger dose of drug per kilogram of body weight than an older child or adult (Collis et al 1990), whereas different-aged children using the BimboNeb would receive a more constant dose per kilogram as the mass output increased with tidal volume.

Very little flunisolide was deposited on the inspiratory filter in the second 5 min of nebulisation, even though the nebuliser was still spluttering and fluid was still present in the nebuliser bowl. From a practical point of view our results suggest that it is not worthwhile nebulising for more than 5 min as very little extra drug is available for inhalation. This is consistent with previous reports with other nebulisers and drugs (O'Callaghan et al 1989; Barry & O'Callaghan 1998; O'Callaghan et al 2000).

Drug collection on filters during the breathing simulation experiments represents all the medication that would be inhaled by the patient, not just that delivered to the lungs. Lung deposition may be estimated by multiplying the filter drug deposition by the fraction of drug below a certain size from the particle sizing experiments. We assume lung deposition is related to aerosol

particle size, and that the cut off here of 4.3 μm, representing the final stage and filter of the impinger, is appropriate for delineating between lung and extrapulmonary deposition. In this paper we quote the drug collected on stages 3, 4 and filter and on stage 4 and filter representing drug in particles smaller than 6.8 μm and 4.3 μm, respectively.

The aim of inhalational drug delivery is to deliver an appropriate amount of drug to the correct site of action in the lungs, with minimal drug delivery to other sites, in a reproducible, rapid and cost-effective manner that is acceptable to the patient. The clinician will only be able to achieve this aim if provided with detailed information on the likely amount of drug released from different drug-delivery devices. This paper provides information on the delivery of an inhaled corticosteroid solution from two different nebulisers. In conjunction with other comparative studies using similar methodology, this information may be used to inform the clinician's choice when selecting an appropriate device and drug for a patient.

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