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# Delivery of nebulized budesonide is affected by nebulizer type and breathing pattern

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## Abstract

The aim of this study was to determine the output in-vitro of budesonide from two different nebulizers under simulated breathing conditions. The BimboNeb and Nebula nebulizers were used to nebulize 2 mL of budesonide (500 $\mu$g) suspension. Particle size was determined by inertial impaction after a 5-min nebulization. Total outputs of the drug from both nebulizers were measured using a sinus flow pump to create simulated breathing conditions. Paediatric and adult breathing patterns were used, with drug output measured after 5 and 10 min nebulization. The mass median aerodynamic diameter of budesonide using the BimboNeb (4.5 $\mu$m) was significantly greater than that from the Nebula (3.4 $\mu$m) ($P < 0.01$). With the simulated adult breathing pattern, the total drug output after 5 min with the BimboNeb (61.5 $\mu$g) was twice that from the Nebula (30.7 $\mu$g). For the paediatric breathing pattern, total outputs were very similar for both nebulizers. In all cases, nebulizing for 10 min produced greater drug outputs compared with those after 5 min, particularly for the paediatric breathing pattern. The amount of aerosolized drug available for inhalation needs to be assessed for each nebuliser used and the effect of the patient's breathing pattern should also be taken into account.

## Introduction

Inhaled steroids play an extremely important part in the treatment of asthma and nebulized budesonide is very effective in the treatment of croup (Husby et al 1993). Although important side effects are uncommon in users of low-dose inhaled steroids, there is concern over the potential effects of high-dose inhaled steroids. In the UK, the Committee on Safety of Medicines concluded that clinically important systemic adverse effects can occur at licensed doses of inhaled corticosteroids with the risk being increased after prolonged high-dose therapy (Committee on Safety of Medicines 1998). Indeed, a recent study by Todd et al (2002) found that the frequency of acute adrenal crisis due to inhaled steroids was much greater than expected in the UK. Understanding the dose of corticosteroid actually inhaled by patients is essential to allow appropriate evaluation of the effect of the dose given and side effects caused.

Information on the dose that is likely to be inhaled from nebulizers is particularly important, given the fact that the choice of device, usually made by the patient or parent, may result in a four-fold difference in the amount of drug inhaled (O'Callaghan & Barry 1999). Even if the same device is used, the dose inhaled will vary depending on the patient's breathing pattern (Barry & O'Callaghan 1999) and the technique they use (Everard et al 1992).

Significant variability may also occur in the percentage of the prescribed, nominal, dose that is inhaled when drugs are delivered in either a solution or in a suspension formulation. This is the case with corticosteroids, where beclomethasone dipropionate and budesonide are nebulized from a suspension, while flunisolide is nebulized from a solution. When comparing drug delivery from different types of nebulizer, the total amount of aerosolized drug available to the patient and the particle size distribution of the aerosol cloud need to be measured. To determine the effect of the patient's breathing pattern on the total dose they inhale, a filter may be interposed between the nebulizer and the patient or a device that simulates the breathing pattern of a patient. The drug trapped on the filter is then assayed to estimate the total drug that is likely to be inhaled. By combining this data with the particle size analysis

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results, one may estimate the amount of drug inhaled that is contained within various particle size fractions. In general, for the delivery of corticosteroids, drug contained in particles $< 5\,\mu$m has been considered ideal for drug delivery to the lung.

We have previously investigated the output of budesonide (Pulmicort; AstraZeneca, Kings Langley, UK) and have shown very significant differences in the output depending on the nebulizer used and the patient's breathing pattern (Barry & O'Callaghan 1999). This study was conducted using the precise methodology and nebulizers used previously to determine the drug delivery of beclomethasone (O'Callaghan et al 2000), a steroid suspension, and a corticosteroid solution, flunisolide (O'Callaghan et al 2002), to allow comparisons of drug delivery. These studies showed significant differences in drug outputs from the nebulizers studied.

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

## Materials and Methods

### Nebulizers and medication

The nebulizers and compressors used were the BimboNeb (Mefar, Bovezzo (BS) Italy) and the Nebula (Markos, Monza (MI), Italy). Airflows through the nebulizers were $4\,\mathrm{L\,min^{-1}}$ and $5\,\mathrm{L\,min^{-1}}$ for the BimboNeb and Nebula, respectively.

A 2-mL ampoule of budesonide suspension $0.25\,\mathrm{mg\,mL^{-1}}$ (Spirocort; Simesa S.p.a., Italy; made under licence for AstraZeneca) was used for each experiment.

### Particle size measurement

The particle size distribution of the aerosol clouds produced by the nebulizers was measured using a glass multistage liquid impinger (MSLI). The MSLI had previously been calibrated with an aerosol of known particle size distribution (Barry 1999). Cut-offs for stages 1–4 were 10.1 $\mu$m, 6.8 $\mu$m, 4.3 $\mu$m and 1.0 $\mu$m and 12.6 $\mu$m for the throat with the airflow through the impinger adjusted to $60\,\mathrm{L\,min^{-1}}$.

Nebulisers were filled with 2 mL of budesonide suspension and the nebulizer mouthpiece was rested against the throat of the MSLI. The amount of drug collected on each part of the MSLI was assayed using high-performance liquid chromatography (HPLC) as previously described (Barry & O'Callaghan 1999). Each nebulizer was tested on four different occasions.

### Effect of breathing pattern

We determined the effect of breathing pattern on drug output by using a breathing pattern simulator (Pari Sinus Breathing Pattern Simulator; Pari, GmbH, Starnberg, Germany). This allows simulated tidal volume, respiratory rate and respiratory time to be independently adjusted. The nebulizers were operated for 5 min under simulated breathing conditions and drug leaving the mouthpiece was trapped on an inspiratory filter. This was an electrostatic filter held in a low-dead-volume filter assembly (11 mL) interposed between the mouthpiece and the breathing simulator. Nebulization was continued for a further 5 min, collecting drug output on a fresh filter. Two different breathing patterns were used – the paediatric pattern (tidal volume of 150 mL, 20 breaths per min and an inspiratory fraction of 40%, which resulted in a minute volume of $3\,\mathrm{L\,min^{-1}}$, a maximum inspiratory flow of $11.8\,\mathrm{L\,min^{-1}}$ and a mean inspiratory flow of $7.5\,\mathrm{L\,min^{-1}}$) and the adult pattern (tidal volume of 600 mL, 12 breaths per min and an inspiratory fraction of 40%, which resulted in a minute volume of $7.2\,\mathrm{L\,min^{-1}}$, a maximum inspiratory flow of $28.3\,\mathrm{L\,min^{-1}}$ and a mean inspiratory flow of $18\,\mathrm{L\,min^{-1}}$).

Each nebulizer was assessed at each breathing pattern on four different occasions. Drug deposited on the 5- and 10-min filters was recovered by dissolution into an appropriate solvent and quantified by HPLC as previously described (Barry & O'Callaghan 1999). The method of drug recovery from the filters was validated and found to be $> 95\%$.

### Statistics

Once the total mass of drug deposited in the MSLI and the mass of drug recovered from each stage were known, the cumulative percentage of drug in particles smaller than the cut-off size of each stage was calculated. Using this data, a log probability plot was prepared and from this the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were determined. The mean and standard deviation of these derived values were calculated for each nebulizer. The MMADs of the clouds produced by the 2 nebulizers were compared using a $t$-test; statistical significance was assumed to be $P < 0.05$.

An overall analysis of the breathing simulation results was performed. A two-way analysis of variance followed by Bonferroni post tests was used to determine whether the type of nebulizer or breathing pattern affected drug output to the filter and if there was any interaction of these two variables.

## Results

There was a significant difference in the particle size of budesonide from the two nebulizers ($P < 0.01$) but no significant difference in the total output to the MSLI ($P > 0.05$). The MMAD and GSD calculated for the aerosol cloud of budesonide from the BimboNeb and Nebula are given in Table 1.

Statistical analysis of the breathing simulator data showed that the breathing pattern significantly affected drug output from the BimboNeb ($P < 0.01$) but not from the Nebula ($P > 0.05$). Using the paediatric breathing pattern the mean (s.d.) amount of drug delivered to the filter after 5 min was 34.0 (14) $\mu$g from the BimboNeb and 33.7 (4.8) $\mu$g from the Nebula (Table 2). Extrapolating from the particle sizing experiment, 16.6 (6.8) $\mu$g

**Table 1** Particle sizing data for budesonide from BimboNeb and Nebula nebulisers

| | BimboNeb | Nebula |
|---|---|---|
| MMAD ($\mu$m) | 4.48 (0.44) | 3.38 (0.38) |
| GSD | 2.25 (0.06) | 2.18 (0.10) |
| Total weight ($\mu$g) in cloud | 119.93 (9.62) | 113.45 (9.54) |
| Amount of budesonide ($\mu$g) contained in particles $<4.3\,\mu$m | 57.93 (5.34) | 73.45 (3.63) |
| % of nominal dose | 11.59 (1.07) | 14.69 (0.73) |
| % of total amount of drug leaving nebuliser in particles $<4.3\,\mu$m | 48.69 (7.30) | 64.97 (4.32) |
| Amount of budesonide ($\mu$g) contained in particles $<6.8\,\mu$m | 78.79 (4.65) | 92.83 (4.69) |
| % of nominal dose | 15.76 (0.93) | 18.57 (0.94) |
| % of total amount of drug leaving nebuliser in particles $<6.8\,\mu$m | 66.07 (7.16) | 82.05 (4.39) |

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

(BimboNeb) and 21.9 (3.1) $\mu$g (Nebula) would have been in particles $<4.3\,\mu$m. Using the adult breathing pattern increased the total drug output from the BimboNeb to 61.5 (11.7) $\mu$g but resulted in a slight decrease with the Nebula to 30.7 (4.6) $\mu$g.

Increasing the nebulization time to 10 min increased the drug output for both nebulisers and both breathing patterns. There was a greater increase with the paediatric breathing patterns at 10 min (40.5 and 35.5% for BimboNeb and Nebula, respectively), compared with the increase seen with the adult breathing pattern (12.1 and 29.6% for BimboNeb and Nebula, respectively).

## Discussion

The results of this study confirm a worrying trend in the delivery of nebulized corticosteroids. That is, depending on the nebulizer chosen, the dose inhaled by the patient may vary considerably. With the BimboNeb, almost twice as much drug was trapped on the inspiratory filter and therefore likely to be inhaled when the adult breathing pattern was used as opposed to the Nebula. Similar amounts of drug were trapped on the inspiratory filter when the paediatric breathing pattern was used. This emphasizes the need for separate paediatric data on drug delivery from nebulizers and that it is inappropriate to extrapolate results from adult studies to children.

Caution is required when comparing in-vitro results between studies as small variations in methodology may result in a marked change in the estimation of drug particle size and the amount likely to be inhaled. Comparisons should not be made between the particle size distribution of a nebulized solution and suspension measured using laser methods. For example, the effect of mixing salbutamol with a corticosteroid in suspension (beclomethasone dipropionate) or in a solution (flunisolide) was recently studied. The investigators used a laser diffraction analyser, the API aerosizer, to measure particle size (Di Berardino & Scaglione 1999). This device is a time-of-flight instrument frequently used to measure the size distribution of an aerosol. It cannot, however, detect which droplets, when a corticosteroid suspension is nebulized, contain a particle of drug. Using the laser method will therefore result in a significant underestimation of the size of the droplets containing the corticosteroid (O'Callaghan & Barry 1997). The use of methods that fractionate the aerosol cloud, allowing assay of the amount of corticosteroid contained in these particle size fractions, is appropriate. The MSLI used in this study allows such measurements to be made.

In previous studies, we have used exactly the same methodology and nebulizers to determine the output of flunisolide solution (O'Callaghan et al 2002) and beclomethasone dipropionate suspension (O'Callaghan et al 2000), allowing us to compare these results to those obtained in this study. Very significant differences were seen depending on the drug used. The MMAD of beclomethasone aerosol produced when nebulized by the BimboNeb (6.4 $\mu$m) and Nebula (5.4 $\mu$m) was much higher than that of flunisolide (BimboNeb 3.9 $\mu$m: Nebula 3.9 $\mu$m) and budesonide (BimboNeb 4.5 $\mu$m; Nebula 3.4 $\mu$m), presumably due to the shape and size of the steroid particles.

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

| | BimboNeb | | Nebula | |
|---|---|---|---|---|
| | Paediatric | Adult | Paediatric | Adult |
| Total drug ($\mu$g) delivered to the filter after 5 min nebulisation | 33.98 (14.02) | 61.50 (11.65) | 33.75 (4.75) | 30.68 (4.62) |
| % of nominal dose | 6.80 (2.80) | 12.30 (2.33) | 6.75 (0.95) | 6.14 (0.92) |
| Amount of budesonide ($\mu$g) contained in particles $<4.3\,\mu$m | 16.55 (6.82) | 29.94 (5.67) | 21.93 (3.09) | 19.93 (3.00) |
| Amount of budesonide ($\mu$g) contained in particles $<6.8\,\mu$m | 22.45 (9.26) | 40.63 (7.69) | 27.69 (3.90) | 25.17 (3.79) |
| Total drug ($\mu$g) delivered to the filter after 10 min nebulisation | 47.73 (6.99) | 68.93 (9.75) | 45.73 (4.06) | 39.75 (2.60) |

s.d. is given in parentheses.

The amount of drug collected on the inspiratory filters in this study represents the total amount of drug likely to be inhaled and 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. Lung deposition is related to aerosol size and in this paper we quote the amount of drug calculated to be contained in particles $< 4.3\,\mu$m and $< 6.8\,\mu$m. Drug deposited on the final stage and filter of the MSLI will be contained in particles $< 4.3\,\mu$m, and drug collected on stages 3, 4 and the filter represent drug in particles $< 6.8\,\mu$m. In a previous study on flunisolide, we have suggested that the cut-off of $4.3\,\mu$m may be appropriate for delineating between lung and extra-pulmonary deposition.

Use of the BimboNeb, which has an active venturi system incorporated into its design, led to an increase in the total dose likely to be inhaled when an adult breathing pattern was used compared with the paediatric pattern, for all of the drugs studied (flunisolide 58%, budesonide 81%, beclomethasone 14%). This was not seen when the Nebula was used (flunisolide 15% increase with adult breathing pattern; budesonide paediatric breathing pattern 10% greater than adult; beclomethasone paediatric breathing pattern 33% greater than adult).

The amount of corticosteroid contained in various particle size ranges likely to be inhaled also varied depending on the drug. The greatest percentage of the nominal dose in particles $< 4.3\,\mu$m, calculated to be available to the patient, was for flunisolide (BimboNeb, adult 8.9%, paediatric 5.6%; Nebula, adult 6.4%, paediatric 5.5%) followed by budesonide (BimboNeb, adult 6%, paediatric 3.4%; Nebula, adult 4%, paediatric 4.3%) and then beclomethasone (BimboNeb, adult 2.3%, paediatric 2%; Nebula, adult 2.2%, paediatric 2.8%).

This trend was also seen in the amount of drug likely to be inhaled over a 5-min period contained in particles $< 6.8\,\mu$m. There was a greater percentage of the initial nominal dose for flunisolide (BimboNeb, adult 12%, paediatric 7.7%; Nebula, adult 8.7%, paediatric 7.6%) followed by budesonide (BimboNeb, adult 8.1%, paediatric 4.5%; Nebula, adult 5%, paediatric 5.5%) and then beclomethasone (BimboNeb, adult 4.3%, paediatric 3.8%; Nebula, adult 3.5%, paediatric 4.8%).

The results of this study and our ability to compare them with previous work confirms the large variability in the dose likely to be inhaled and the amount of drug that is inhaled in particles likely to be deposited in the lower respiratory tract. It also highlights the relatively low efficiency of the nebulizers studied when used with corticosteroid suspensions, with relatively small percentages of the prescribed dose being inhaled and subsequently reaching the lungs.

In summary, particle size was significantly affected by the nebulizer choice, being significantly smaller for the Nebula than the BimboNeb. However, adults inhaling from the BimboNeb are likely to inhale twice as much drug than when inhaling from the Nebula. These results cannot be extrapolated to children as the amount likely to be inhaled by a child was similar for both nebulizers.

## References


Barry, P. W. (1999) *Problems with inhalational drug delivery*. PhD Thesis, University of Leicester

Barry, P. W., O'Callaghan, C. (1999) An in vitro analysis of the output of budesonide from different nebulisers. *J. Allergy Clin. Immunol*. **184**: 1168–1173

Committee on Safety of Medicines (1998) Focus on corticosteroids. *Curr. Probl. Pharmacovigilance* **24**: 5–10

Di Berardino, L., Scaglione, F. (1999) Mixing albuterol and corticosteroid is not additive. *Allergy* **54**: 1012–1013

Everard, M. L., Clark, A. R., Milner, A. D. (1992) Drug delivery from jet nebulisers. *Arch. Dis. Child*. **67**: 586–591

Husby, S., Agertoft, L., Mortensen, S., Pedersen, S. (1993) Treatment of croup with nebulised steroid (budesonide): a double blind, placebo controlled study. *Arch. Dis. Child*. **68**: 352–355

O'Callaghan, C., Barry, P. (1997) The science of nebulised drug delivery. *Thorax* **52** (Suppl. 2): S33–S44

O'Callaghan, C., Barry, P. W. (1999) Delivering inhaled corticosteroids to patients: if side effects are important, why are we so ignorant of the dose inhaled? *Br. Med. J*. **318**: 410–411

O'Callaghan, C., White, J., Barry, P. W., Kantar, A. (2000) Analysis of the output of beclomethasone dipropionate from different nebulisers. *Riv. Ital. Pediatr. (IJP)* **26**: 821–824

O'Callaghan, C., White, J., Jackson, J., Barry, P., Kantar, A. (2002) The output of flunisolide from different nebulisers. *J. Pharm. Pharmacol*. **54**: 565–569

Todd, G. R. G., Acerini, C. L., Ross-Russell, R., Zahra, S., Warner, J. T., McCance, D. (2002) Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch. Dis. Child*. **87**: 457–461