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Nebulisation of corticosteroid suspensions and solutions with a β_2 agonist

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Abstract

The aim of this study was to determine the output of salbutamol nebulised in combination with either flunisolide or beclometasone dipropionate (BDP) from two different nebulisers under simulated breathing conditions. The BimboNeb and Nebula nebulisers were used to nebulise 3.0 mL of the two drug mixtures (salbutamol, 5000 μg plus either flunisolide, 600 μg, or BDP, 800 μg). Particle size was determined by inertial impaction. Total outputs of all drugs from both nebulisers were measured using a sinus flow pump under simulated paediatric and adult breathing patterns. The mass median aerodynamic diameter (MMAD) of BDP particles from the mixture was 6.34 μm using the BimboNeb and 5.34 μm using the Nebula. Values for salbutamol in this mixture were 3.93 and 3.32 μm, respectively. The MMAD of flunisolide particles from the BimboNeb and Nebula were 3.74 and 3.65 μm, respectively, while for salbutamol were 3.79 and 3.74 μm, respectively. With the simulated adult breathing pattern, all drug outputs from both mixtures were greater from the BimboNeb than from the Nebula after 5 and 10 min' nebulisation. Drug delivery from the BimboNeb, but not the Nebula, was affected by the simulated breathing pattern. Outputs with the BimboNeb were lower with the paediatric breathing pattern than with the adult pattern. In the majority of cases, nebulising for 10 min produced significantly greater drug output than after 5 min. For the Nebula, outputs were generally similar at 5 and 10 min, irrespective of the breathing pattern. These results highlight the need to assess the amount of aerosolised drug available when drugs are combined, when different nebulisers are used and when they are used with patients of different ages.

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Introduction

The addition of an inhaled long-acting β_2 agonist to an inhaled corticosteroid gives good control of asthma in most patients, and it has been argued that combination inhalers (formoterol/budesonide and salmeterol/fluticasone) may optimise the beneficial actions of each individual drug in the airways (Barnes 2002).

Corticosteroids given by nebulisation are still commonly prescribed to patients with asthma. A combined preparation of a corticosteroid and long-acting bronchodilator for nebulisation is not currently available; however, corticosteroids are often nebulised in combination with a short-acting β_2 agonist. This practice was developed to reduce nebulisation time, and recent data supporting the benefits of combining β_2 agonists and corticosteroids are likely to increase such usage. It is of concern, however, that there are no data on the effect of mixing and then nebulising a β_2 agonist and a corticosteroid suspension or solution on the amount of each drug released by the nebuliser. Such data are important, however, as the nominal dose of a drug placed in a nebuliser often bears little resemblance to the dose emitted, which can vary considerably depending on the nebuliser used and breathing pattern of the patient (Barry & O'Callaghan 1998a). The choice of a corticosteroid suspension or solution may also significantly affect the drug delivered (O'Callaghan et al 2000, 2002). When assessing drug delivery from nebulisers, it is also essential to take into account the breathing pattern of the patient, as this may significantly affect the dose of drug they receive (Collis et al 1990).

The aim of this study was to estimate the amount of drug contained in particles likely to reach the lungs, and the total amounts of flunisolide and salbutamol combined and beclometasone diproprionate (BDP) and salbutamol combined that would be inhaled by children

and adults from two commonly used nebulisers. Flunisolide was chosen as an example of a steroid in solution and BDP as a steroid suspension. We also describe the HPLC methods developed to enable measurement of corticosteroids and salbutamol concentrations from the same mixture, allowing us to determine their output from the nebulisers studied.

Methods

Nebulisers and medication

The nebulisers and compressors used were the BimboNeb (Mefar, Bovezzo (BS) Italy) and the Nebula (Markos, Monza (MI) Italy). The salbutamol/BDP mixture was prepared by adding 1 mL salbutamol (5000 μg) (Bronchovaleas; Valeas s.p.a. Pharmaceuticals, Milan, Italy) to the contents of a 2 mL respule of BDP (800 μg) suspension (Clenil A; Chiesi, Parma, Italy). The salbutamol/flunisolide mixture was prepared by adding 1 mL salbutamol (5000 μg) solution and 0.6 mL (600 μg) flunisolide solution (Lunibron A; Valeas s.p.a. Pharmaceuticals, Milan, Italy) to 1.4 mL 0.9% saline. Both mixtures had a final volume fill of 3 mL.

The compositions of the drug mixtures used in this study were as follows. Bronchovaleas salbutamol (5 mg mL^{-1}) consisted of salbutamol, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate and water. BDP suspension was composed of BDP (0.4 mg mL^{-1}), sodium dihydrogen phosphate dihydrate, sodium chloride, potassium hydrogen phosphate, benzyl alcohol, methyl p-hydroxybenzoate, cetostearyl alcohol, polysorbitan 20, sorbitan monolaurate, propyl p-hydroxybenzoate and pure water. Lunibron (100 mL) contained flunisolide (100 mg), propylene glycol (50 mL), sodium chloride (450 mg) and water (50 mL).

Measurement of particle size

The particle-size distribution of each drug in the aerosol clouds was measured using a four-stage glass multistage liquid impinger (MSLI; Scientific Glass, Nottingham, UK) as described previously (O'Callaghan et al 2000). Nebulisers were charged with 3 mL of mixture and operated for 5 min. The nebulisers and each stage of the MSLI were washed with an appropriate solvent to recover both drugs. The two drugs were quantified simultaneously using fully validated HPLC methods (see below). Each nebuliser/drug mixture combination was tested four times.

Breathing simulation

Total drug output from the nebulisers was measured under simulated breathing conditions as described previously (O'Callaghan et al 2000). Nebuliser drug outputs were deposited on an inspiratory filter (an electrostatic pad in a holder with low dead volume) positioned between the breathing simulator and the nebuliser. As in previous studies, drug output was measured using two different breathing patterns: paediatric and adult. The tidal volume, respiratory rate and inspiratory fraction were 150 mL, 20 breaths min^{-1} and 40%, respectively, for the paediatric breathing pattern, and 600 mL, 12 breaths min^{-1} and 40%, respectively, for the adult breathing pattern. Waste aerosol released during simulated expiration was collected on an expiratory filter. Nebulisers were charged with 3 mL of mixture and operated for 5 min with the nebuliser mouthpiece connected to the filter assembly. After 5 min, nebulisation was stopped and both filters were changed. Nebulisation was re-commenced for a further 5 min (total 10 min). Drug remaining in the nebuliser and deposited on the 5 and 10 min filters was recovered by dissolution into an appropriate solvent and quantified by HPLC. The method of drug recovery from the filters was validated and found to be > 95% in all cases. Each nebuliser/drug mixture combination was tested four times with each breathing pattern.

HPLC methods

New HPLC methods were developed to allow simultaneous determination of both drugs from each mixture during a single chromatography run using an internal standard method. The HPLC column was a Spherisorb ODS1, 5 μm particle size, 100 mm × 4.6 mm (Waters, Elstree, UK) for both methods. To separate salbutamol and BDP, the mobile phase consisted of methanol and 0.2% ammonium acetate (68:32) at a flow rate of 1.7 mL min^{-1} and a column temperature of 40°C; testosterone propionate was used as the internal standard. For the separation of salbutamol and flunisolide, the mobile phase was methanol and 0.1% ammonium acetate (71:29) at a flow rate of 2 mL min^{-1} and a column temperature of 30°C; benzyl biphenyl was used as the internal standard. A UV detection wavelength of 239 nm was used for both assays.

Statistical methods

The total mass of each drug deposited in the MSLI and the percentage in each of its four stages were calculated. The 50% cut-off diameter for each stage was known and the cumulative percentage of each drug less than this diameter was calculated. A log probability plot of aerodynamic size against cumulative percentage of drug undersize was constructed for each drug, from which the mass median aerodynamic diameter (MMAD) and geometric standard deviation were derived. The percentage of particles less than 4.3 μm was calculated as the total drug in stage 4 plus the filter, and the percentage of particles less than 6.8 μm as the total drug in stages 3 and 4 plus the filter. For comparative purposes, mass outputs from the nebulisers under simulated breathing conditions were calculated as percentage nominal dose for each drug.

Results are expressed as a mean (± s.d.) of four experiments. Particle size data were compared using the Mann–Whitney U test. Mass drug outputs for the different drug/nebuliser combinations and breathing patterns were compared using two-way analysis of variance followed by Bonferroni tests.

Results

Tables 1 and 2 summarise the particle size characteristics of the drug clouds produced when the salbutamol/BDP and salbutamol/flunisolide mixtures were nebulised under constant-flow conditions

Table 1 Particle-sizing data for the salbutamol/BDP mixture from BimboNeb and Nebula nebulisers

	BimboNeb		**Nebula**	
	Salbutamol	BDP	Salbutamol	BDP
MMAD (μm)	3.93 (0.22)	6.34 (0.27)	3.32 (0.19)	5.34 (0.40)
GSD	2.43 (0.09)	1.80 (0.05)	2.54 (0.05)	1.95 (0.06)
Total weight of drug in cloud (μg)	2697 (189)	289 (31.1)	1863 (124)	172 (24.9)
Proportion of drug leaving nebuliser in particles < 4.3 μm (%)	51.1 (2.8)	29.1 (3.6)	58.0(2.5)	38.5 (4.2)
Proportion of drug leaving nebuliser in particles < 6.8 μm (%)	68.6 (2.3)	51.4 (2.0)	76.4 (1.9)	63.8 (4.1)

MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation.
Data are mean (s.d.) of four measurements.

Table 2 Particle-sizing data for the salbutamol/flunisolide mixture from BimboNeb and Nebula nebulisers

	BimboNeb		**Nebula**	
	Salbutamol	Flunisolide	Salbutamol	Flunisolide
MMAD (μm)	3.79 (0.25)	3.74 (0.24)	3.74 (0.18)	3.65 (0.22)
GSD	2.24 (0.08)	2.28 (0.10)	2.21 (0.04)	2.26 (0.02)
Total weight of drug in cloud (μg)	1918 (364)	243 (44.1)	2087 (68)	264 (11.2)
Proportion of drug leaving nebuliser in particles < 4.3 μm (%)	50.3 (4.6)	51.7 (4.6)	48.5 (2.7)	50.2 (3.2)
Proportion of drug leaving nebuliser in particles < 6.8 μm (%)	74.1 (3.6)	74.7 (3.3)	72.5 (2.4)	73.7(2.7)

MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation.
Data are mean (s.d.) of four measurements.

using the BimboNeb and Nebula. When salbutamol and BDP were nebulised together, using either nebuliser, the MMAD was significantly smaller for salbutamol than BDP ($P < 0.05$ for BimboNeb; $P < 0.01$ for Nebula).

With the same drug combination, the percentage of drug released in small particles (< 4.3 μm) was significantly greater for salbutamol than BDP ($P < 0.05$ for BimboNeb; $P < 0.01$ for Nebula).

The MMADs calculated for both drugs were larger following nebulisation by the BimboNeb, as was the total drug output of both salbutamol and BDP ($P < 0.05$). However, when flunisolide was nebulised with salbutamol, a similar proportion of each drug in the cloud was in small particles (< 4.3 μm) and the MMAD calculated for salbutamol and flunisolide was similar with the two nebulisers. The total drug output was also similar for both salbutamol and flunisolide. In all cases, drug recovery from the MSLI and nebuliser was over 94%.

The total amounts of the drugs (expressed as the percentage of the nominal dose) delivered to a filter placed between the nebuliser and breathing simulator represents the total amount of drug likely to be inhaled by a patient with the same breathing patterns; these are shown in Figures 1 and 2.

Using the adult breathing pattern, the outputs of BDP and salbutamol from the mixture were higher from the BimboNeb than from the Nebula after 5 min and 10 min' nebulisation ($P < 0.01$; $P < 0.001$, respectively).

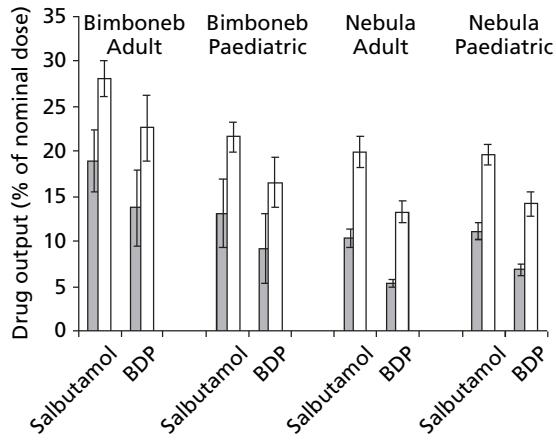

Figure 1 Breathing simulation data for a mixture of salbutamol and BDP nebulised using two different nebulisers and adult and paediatric breathing patterns. The amount of each drug deposited on the filter is shown as a percentage of the nominal dose. Each bar represents the mean (± s.d.) of four measurements. Grey and white bars represent drug deposited after 5 min and 10 min' nebulisation, respectively.

The effect of breathing pattern on drug output was different for the two nebulisers. Using the adult breathing pattern, the BimboNeb delivered a mean of 181 μg (s.d. 29.4) of BDP and

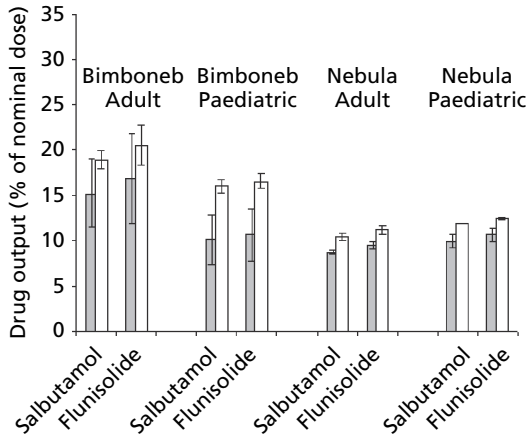

Figure 2 Breathing simulation data for a mixture of salbutamol and flunisolide nebulised using two different nebulisers and adult and paediatric breathing patterns. The amount of each drug deposited on a filter is shown as a percentage of the nominal dose. Each bar represents the mean (± s.d.) of four measurements. Grey and white bars represent drug deposited after 5 min and 10 min' nebulisation, respectively.

1406 μg (105) of salbutamol to the filter in 10 min, which was slightly more than the 132 μg (22.4) of BDP delivered using the paediatric breathing pattern and significantly more than the 1083 μg (84.4) of salbutamol ($P<0.01$). The outputs of BDP and salbutamol from the Nebula were similar after 5 min and 10 min, whichever breathing pattern was used.

Using the adult breathing pattern and the salbutamol/flunisolide mixture, the outputs of both drugs were significantly higher from the BimboNeb than from the Nebula after 5 min and 10 min nebulisation ($P<0.01$, $P<0.001$, respectively). Using the paediatric breathing pattern, both nebulisers delivered a similar amount of flunisolide and salbutamol to the filter in 5 min, but after 10 min the BimboNeb delivered significantly more of both drugs ($P<0.01$ for flunisolide; $P<0.001$ for salbutamol). Using the adult breathing pattern, the BimboNeb delivered 123 μg (13.3) of flunisolide and 943 μg (51.7) of salbutamol to the filter in 10 min, which was slightly more than the 99.5 μg (4.8) of flunisolide and 802 μg (36.4) of salbutamol delivered using the paediatric pattern. The Nebula delivered slightly more flunisolide and salbutamol to a filter in 10 min using the paediatric breathing pattern compared with the adult breathing pattern.

Increasing the nebulisation time from 5 min to 10 min caused a substantial increase in the outputs of both drugs from the salbutamol/BDP mixture, for both nebulisers. For the salbutamol/flunisolide mixture, increasing nebulisation time had less effect on output, particularly for the Nebula.

Discussion

Inhaled steroids play a vital role in the management of asthma, and are used as first-line prophylactic agents for both children and adults (British Thoracic Society 1997). Although important side-effects are rare with low doses of inhaled steroids, there are concerns over the potential effects of high-dose inhaled steroids (Todd et al 2002a). In 1998, the Committee on Safety of Medicines (CSM) in the UK concluded that clinically important systemic adverse effects can occur at licensed doses of inhaled corticosteroids (CSM & MHRA 1998). A major problem exists, however, in assessing clinical trials of inhaled steroids because the dose that patients who experience side-effects are likely to have inhaled is rarely evaluated. This is of concern as it may bear little resemblance to the prescribed 'nominal' dose. Major differences in the dose inhaled may occur between different drug delivery devices (Barry & O'Callaghan 1999). We have previously shown that the dose of budesonide that a 10-year-old patient is likely to inhale from a breath-enhanced open-vent nebuliser is four times that available from an open-vent device and twice that available from a conventional nebuliser (O'Callaghan & Barry 1999). However, patients and parents who are buying a nebuliser, and health professionals who prescribe the drugs, are usually unaware that the dose of drug inhaled may vary by a factor of four depending on their choice of nebuliser.

In this paper, we have examined the effect of nebulising inhaled corticosteroids mixed with the β_2 agonist salbutamol. While such clinical practice is not uncommon, the effect on drug output of either the steroid or the β_2 agonist has not previously been reported. To allow us to determine drug output from this combination, we developed HPLC methods that allowed the aerosol collected to be assayed simultaneously for the corticosteroid and salbutamol. The study was divided into two parts. First was the estimation of the total amount of β_2 agonist and corticosteroid leaving the nebulisers and the amount of each drug contained in various particle size fractions. As the breathing pattern of patients may have a profound effect on the dose they are likely to inhale from a nebuliser, the effect of adult and paediatric breathing patterns on the total doses of the drugs likely to be inhaled was also determined.

Corticosteroid preparations for nebulisation are usually formulated as suspensions, with the exception of flunisolide, which is available as a solution. Nebulisation of suspensions is significantly different from that of solutions, as, when nebulised, a corticosteroid particle is surrounded by an envelope of carrier fluid. This may result in fewer corticosteroid particles being able to escape from the nebuliser because of their 'enhanced' size, with those particles that do escape tending to be relatively large. Indeed, early attempts to nebulise a 50 μg mL^{-1} suspension of BDP resulted in little drug being released in particles small enough to enter the lung (O'Callaghan 1990) and a poor clinical response (Storr et al 1986; Webb et al 1986). One way to increase the amount of BDP likely to be delivered is to increase the drug concentration. The more concentrated suspension of BDP that is commercially available was therefore used in this study. Increasing the concentration may also have an effect on particle-size, however, although this was not determined in this study. Previous work had shown that the nebulisation of 2 mL of a formulation containing 400 μg mL^{-1} BDP resulted in an aerosol cloud with a MMAD of 6.4 μm for the BimboNeb and 5.4 μm for the Nebula (O'Callaghan et al 2000).

When BDP and salbutamol were nebulised as a mixture, the percentage of each drug in small droplets (< 4.3 μm) was much higher for salbutamol than for BDP, and was also

affected by the choice of nebuliser. This difference may be explained by the fact that when BDP particles are nebulised they are only contained in a few of the aerosol particles leaving the nebuliser. The particles of BDP are surrounded by a fluid envelope that is likely to increase the droplet size further. Droplets that do not contain BDP are likely to be more numerous and smaller, and are made up of the 'carrier' solution of salbutamol.

Another way to improve the delivery of nebulised corticosteroids to the lung is to improve the solubility of a drug by adding a co-solvent and/or other additives such as surfactants or buffers (O'Callaghan & Barry 1997). Drug output and the percentage of drug contained in small particles are normally greater from a solution than a suspension. The flunisolide formulation (Lunibron A) used in this and our previous studies (O'Callaghan et al 2002) contains propylene glycol, which acts as a co-solvent to promote the dissolution of the flunisolide. The particle size characteristics of the flunisolide cloud from the BimboNeb and Nebula were almost identical, with an MMAD of 3.9 μm, and approximately 60% of the drug released in particles smaller than 4.3 μm. Only 19% of the drug was contained in particles larger than 6.8 μm, which suggests that the oropharyngeal deposition may be lower than for BDP. As expected when nebulising the combined solution of salbutamol and flunisolide, there was no difference in particle size for the two drugs.

The outputs of BDP and flunisolide from the BimboNeb and Nebula have been measured previously using the same methodology as in the present study (O'Callaghan et al 2000, 2002). Although the results are not directly comparable because of the combination of salbutamol with the corticosteroids and the larger volume fills, the MMADs of the steroid particles were similar (O'Callaghan et al 2000, 2002). This suggests that combining the steroids with salbutamol has little effect on the particle size of the steroid aerosol produced.

Lung deposition of inhaled medications is known to be affected by both patient factors and the delivery device. The dose of medication that reaches the airways may be affected by nebuliser type, fill volume and the driving gas flow (Hess et al 1996), breathing pattern (Barry & O'Callaghan 1998b) and even the distance of the nebuliser from the face when a facemask is used (Everard et al 1992). In this study, we evaluated the effect of breathing pattern on the dose captured on a filter between the nebuliser and the breathing simulator machine. For both nebulisers and both the adult and paediatric breathing patterns, slightly more salbutamol was delivered to the breathing simulator filter in 5 min when mixed with BDP compared with when mixed with flunisolide. Extending the nebulisation time to 10 min significantly increased the output of salbutamol to the filter in the majority of cases. This increase was less significant with the Nebula for both breathing patterns when salbutamol was co-nebulised with flunisolide. As can be seen from the results section, the drug output from the two nebulisers could not be predicted, and varied with each device and with the breathing pattern used.

Conclusion

The results of this study suggest that salbutamol can be nebulised with corticosteroid suspensions and solutions. However, it is impossible to estimate the dose that the patient is actually likely to inhale from the prescribed nominal dose unless the combination of drugs and nebulisers is tested in association with the breathing pattern of the patients likely to use the nebuliser. We argue that detailed information should be made available to clinicians on the dose of drug that is likely to be inhaled by their patient for each nebuliser drug combination. Failure to do this is to accept that children and adults with asthma may receive significantly different doses of steroid or β_2 agonist without anyone being aware.

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