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Relative lung deposition of salbutamol following inhalation from a spacer and a Sidestream jet nebulizer following an acute exacerbation

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Studies have shown that a large volume spacer attached to a metered dose inhaler provides similar bronchodilator effects to nebulized dosing during the management of patients following an acute exacerbation.
- Due to the high doses used, these effects could be measured at the top of the dose–response relationship and the response limited due to the patient's exacerbation.
- Although clinical end-points are the gold standard to show comparability, some indication of similar lung deposition is useful to consolidate any claims.

WHAT THIS STUDY ADDS

- The urinary pharmacokinetic method we have used postinhalation provides an index of lung deposition for inhalation methods that can be incorporated into the routine management of patients with an acute exacerbation.
- This is the first study to identify and compare lung deposition and systemic delivery for inhalation methods within the setting of the routine management of asthma and chronic obstructive pulmonary disease patients following hospitalization due to an acute exacerbation.
- The study highlights the comparability of the doses for the two inhalation methods evaluated with respect to lung deposition, systemic delivery and bronchodilator response.

BACKGROUND

Studies comparing inhalation methods in acute exacerbations have not assessed lung deposition.

METHODS

Five 100-μg salbutamol doses were inhaled from a metered dose inhaler plus spacer (MDI + SP) and 5 mg was nebulized (NEB) following acute exacerbation hospitalization. Urinary salbutamol excretion was determined at 30 min (USAL0.5) and over 24 h (USAL24) postinhalation together with forced expiratory volume in 1 s (FEV_1).

RESULTS

The USAL0.5 mean ratio (90% confidence interval) post MDI + SP and NEB [$n = 19$ asthma, 11 chronic obstructive pulmonary disease (COPD)] was 1.01 (0.81, 1.26). USAL24 was less ($P < 0.001$) following MDI + SP, whereas FEV_1 was similar. Only a small difference between asthmatics and COPD patients was observed for the MDI + SP in that the USAL0.5 was higher in the asthmatics for the spacer method.

CONCLUSION

The relative lung deposition after inhaling 500 μg salbutamol from MDI + SP is similar to 5 mg from a Sidestream nebulizer following an acute exacerbation.

Introduction

Reviews have revealed clinical equivalence for the delivery of bronchodilators to the lungs from a metered dose inhaler (MDI) attached to a large volume spacer and a jet nebulizer [1]. The studies have used outcomes that focus on spirometry. However the lack of sensitivity when using bronchodilator end-points has been shown in a study using one 100-μg dose inhaled from a MDI and a MDI attached to a spacer in 10 stable asthmatics [2]. The bronchodilator response was similar, but lung deposition, measured using gamma scintigraphy, was 12.8 and 23.1%, respectively.

The urinary excretion of salbutamol in the first 30 min (USAL0.5) has been shown to be a useful index to determine the relative bioavailability of an inhalation to the lungs [3]. Furthermore, the urinary excretion of salbutamol and its metabolite over the 24-h period postinhalation is a useful index to compare the relative total systemic delivery between different inhalation methods [3]. Using urinary salbutamol excretion and spirometry, we have compared dosing from a MDI attached to a large volume spacer and a jet nebulizer after hospitalization due to an acute exacerbation.

Patients and methods

Local hospital research ethics committee approval was obtained and all patients gave signed informed consent. Patients with asthma or with chronic obstructive pulmonary disease (COPD) hospitalized following an acute exacerbation and showing no signs of acute respiratory distress or failure were recruited. Those giving signed informed consent were prescribed terbutaline as their β_2-agonist medication.

On the second and fourth day of their admission their terbutaline dose was replaced by a salbutamol study dose. The salbutamol study doses were either five separate 100-μg doses inhaled from a MDI (Ventolin Evohaler™; GlaxoSmithKline, Brentford, UK) attached to a Volumatic™ (GlaxoSmithKline) large volume spacer (MDI + SP) or 5 mg in 2.5 ml (Ventolin Respiratory Solution™; GlaxoSmithKline), diluted to 4 ml with normal saline for nebulization, and nebulized to spluttering using a Sidestream™ chamber (Respironics, Tangmere, UK) driven by a Portaneb™ (Respironics) compressor (NEB). All spacers were prewashed using household detergent, then rinsed in cold water and allowed to air-dry overnight before each study dose. Patients were trained how to use each inhalation method immediately before the study dose.

The inhalation method to be used on the study days was randomized. Thirty minutes after the start of each study dose, patients provided a urine sample (USAL0.5) and then pooled their urine over the next 24 h (USAL24). Urine samples were assayed [3] for their salbutamol and the salbutamol ester sulphate metabolite using high-performance liquid chromatography (HPLC). The salbutamol remaining in each nebulizer chamber and spacer was rinsed and the salbutamol content determined by HPLC. Forced expiratory volume in 1 s (FEV_1) was measured and recorded before each study dose and then at 0.5, 1, 2, 3 and 5 h postinhalation.

In vitro characterization of the emitted dose from MDI + SP was carried out according to standard Pharmacopoeial methodology. Similar values for the nebulizer were determined using the European Standardization Centre (CEN) method, prEN13544-1 [4]. Parameters measured were the amount available for inhalation, the fine particle fraction (particles <5 μm), the mass median aerodynamic diameter (MMAD) and the geometric standard deviation.

The mean difference [95% confidence interval (CI)] was calculated to compare the two inhalation methods within each group and between the asthmatic and COPD patients. Also, USAL0.5 for all the patients was log transformed, and from the mean square error of the ANOVA the mean ratio (90% CI) was calculated, using patients and inhalation method as the main factors.

Results

Nineteen (12 female) asthmatic and 11 (five female) COPD patients completed the study. Their mean (SD) age was 53.7 (17.1) and 63.1 (8.6) years with percentage predicted FEV_1 values on admission of 34.3 (14.5) and 19.2 (6.6)%.

Urinary salbutamol excretion and amounts left in the inhalation device are described in Table 1. The mean (SD) USAL0.5 for all 30 patients following MDI + SP and NEB was 14.1 (7.8) and 14.2 (8.1) μg with a mean ratio (90% CI) of 1.01 (0.81, 1.26). These respective values were 2.82 (1.57) and 0.28 (0.16)% nominal dose with a mean difference (95% CI) of 2.64% (1.97, 3.15; $P < 0.001$). The mean (SD) USAL24 for all 30 patients post MDI + SP and NEB was 194.3 (49.4) and 254.9 (47.2) with a mean difference (95% CI) of –60.6 μg (–76.5, –44.7; $P < 0.001$).

Statistical analysis of USAL0.5 revealed no difference between study days 2 and 4 for the asthmatics and the COPD patients. There was no significant difference between asthma and COPD patients for either inhalation method.

The *in vitro* characterization of the emitted dose is presented in Table 2.

Discussion

The urinary pharmacokinetic method does not interfere with the routine management of patients. Other methods of lung deposition cannot be as routinely applied to situations of acute exacerbations. Thus, this is the first report to

Table 1

Mean (SD) fate of the salbutamol doses and FEV_1 measurements

	ASTHMA MDI + SP	NEB	COPD MDI + SP	NEB
USAL0.5 (μg)	14.7 (7.2)	14.1 (7.6)	13.1 (9.1)	14.4 (9.2)
USAL0.5 (% nominal dose)	2.94 (1.45)	0.28 (0.15)*	2.63 (1.82)	0.29 (0.18)*
USAL24 (μg)	194.0 (53.4)	251.8 (55.1)*	194.7 (43.9)	260.2 (30.6)*
Salbutamol left in device (μg)	231.3 (47.6)	3117 (414)*	229.9 (32.3)	3137 (190)*
Salbutamol dose emitted (μg)	268.7 (47.6)	1883 (413.5)*	270 (32.3)	1863 (190)*
USAL0.5 (% dose emitted)	5.74 (2.99)	0.79 (0.51)*	4.89 (3.26)	0.77 (0.49)*
Predose FEV_1 (% predicted)	42.2 (15.6)	46.9 (18.2)†	27.2 (12.5)	24.1 (9.7)
% FEV_1 increase 60 min postdose‡	9.6 (12.4)	6.5 (7.7)	2.6 (3.3)	4.3 (4.8)

*$P < 0.001$, otherwise not significant. †$P < 0.05$. ‡60 min chosen as this time point provided the highest FEV_1 values. FEV_1, Forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; MDI + SP, metered dose inhaler plus spacer; USAL0.5, urinary salbutamol excretion determined at 30 min; USAL24, urinary salbutamol excretion determined at 24 h.

Table 2

Mean (SD) *in vitro* aerodynamic characteristics of the emitted dose

	MDI + SP	NEB
***In vitro* emitted dose (μg)**	237.2 (8.8)	1649.5 (49.1)
% Fine particle fraction	44.0 (2.4)	80.1 (2.0)
Fine particle dose (μg)	104.1 (3.9)	1321.2 (39.3)
MMAD (μm)	2.8 (0.1)	2.2 (0.4)
GSD	1.7 (0.1)	3.45 (1.1)

MDI + SP, Metered dose inhaler plus spacer; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation

compare the relative deposition for inhalation methods as patients recover from an acute exacerbation. The overall 90% CIs of the USAL0.5 ratio are very close to classical bioequivalence limits of 80–125% for AUC data. Since there is more variability with urinary salbutamol excretion than plasma concentrations [5], a claim for similar relative lung deposition between the two inhalation methods could be justified. Hence, five doses from a MDI attached to a volumatic spacer provides comparable lung deposition to 5 mg nebulized from a Sidestream jet nebulizer in patients with asthma or COPD during recovery from an acute exacerbation.

The small changes in the FEV_1 postinhalation in the asthmatics (<10%), and to some extent in those with COPD (<5%), reflect the severity of their acute exacerbation. The similar bronchodilator effects between the two inhalation methods are comparable to those previously reported during acute exacerbations [1]. Only a small difference between asthmatics and COPD patients was observed for the MDI + SP, in that the USAL0.5 was higher in the asthmatics for the spacer method. This trend was similar to the report by Lipworth and Clark [6] that lung deposition is related to airway calibre in asthmatic patients. This was not the case for the use of nebulizer and could be related to COPD patients being more familiar with this dosing method.

The output from the jet nebulizer is continuous, and since the inhalation:exhalation ratio of these patients would be about 1 : 3, then from the dose available for inhalation (in Table 1) this translates to approximately twice the dose emitted from the spacer and is the most likely explanation of why USAL24 (an index of systemic delivery) is less for the MDI + SP dosing method. The fine particle dose from NEB dosing is about 80% of the emitted dose compared with 44% for the spacer. This suggests that the fine particle dose inhaled by the patient would be much greater than that emitted from the spacer. In addition, the MMAD from NEB dosing is smaller. Despite these more favourable lung deposition aerodynamic characteristics for NEB dosing (higher fine particle dose and smaller MMAD), the relative lung deposition between the two methods was similar. This is due in part to inhalation of the dose from a static cloud in a spacer, issues relating to *in vitro* and *in vivo* correlations and dose emission effects during patient use. The explanation may be due to the *in vitro* methodology. The CEN method, recommended for nebulizers, has not been fully validated, and to determine the particle size distribution only a fraction of the emitted dose is sampled. In fact, only a mean of 72 μg of the emitted dose was sampled in the Marple 298 Cascade Impactor, and 80% of this contained particles sized <5 μm. The limited sampling is due to the small size of the impactor. Although the main purpose of the CEN methodology is to compare different methods, it would be useful to understand the implications of the results with respect to patient management. It is important, therefore, that through validation of the CEN methodology is carried out. This should include an evaluation of the effect of temperature and humidity, because these may be the reason for the low MMAD values. Other cascade impactors may provide more useful information that could reflect the clinical situation, and thus these should also be studied in more detail.

Conclusion

During the recovery of patients with either asthma or COPD from an acute exacerbation, the relative lung deposition (USAL0.5) following inhalation of five 100-µg salbutamol doses from a MDI attached to a large volume spacer (one dose per slow vital capacity inhalation) was similar to 5 mg from a jet nebulizer. The slightly reduced systemic delivery (USAL24) following inhalation from the MDI would decrease the incidence of local and systemic side-effects.

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