

## Lung delivery of salbutamol by dry powder inhaler (Turbuhaler®) and small volume antistatic metal spacer (Airomir® CFC-free MDI plus NebuChamber®)

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*Lung delivery of salbutamol by dry powder inhaler (Turbuhaler®) and small volume antistatic metal spacer (Airomir® CFC-free MDI plus NebuChamber®). B.J. Lipworth, D.J. Clark.*

**ABSTRACT:** As a worldwide ban on the use of chlorofluorocarbons (CFCs) in inhaler devices approaches, considerable attention has been focused on the production of CFC-free delivery devices. The aim of our study was to compare the delivery of salbutamol by dry powder inhaler (DPI), Turbuhaler® and a CFC-free metered-dose inhaler (MDI), Airomir®, used with a novel small volume metal spacer (NebuChamber®).

Ten healthy volunteers, mean (SEM) age 21 (0.7) yrs were studied in a randomized, single (investigator)-blind cross-over design. Single doses of 1,200 µg salbutamol, from Turbuhaler® DPI and Airomir® CFC-free MDI via a NebuChamber®, were given as 12 sequential 100 µg inhalations over 6 min. The lung delivery of salbutamol was assessed by measuring the plasma salbutamol profile over the first 20 min after inhalation. Plasma salbutamol concentration was expressed as maximal ( $C_{max}$ ) and average ( $C_{av}$ ) value.

Significant differences ( $p < 0.001$ ) were found between the NebuChamber® (N) and the Turbuhaler® (T) for salbutamol  $C_{max}$  and  $C_{av}$ . This amounted to a 1.89 fold difference (95% CI 1.56–2.22) between these devices for  $C_{max}$ , and a 1.78 fold difference (95% CI 1.42–2.15) for  $C_{av}$ .

We have demonstrated that, *in vivo*, salbutamol from a chlorofluorocarbon-free metered-dose inhaler given via a small volume metal spacer (NebuChamber®) produces significantly greater delivery than from an efficient dry powder inhaler (Turbuhaler®).

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As a worldwide ban on the use of chlorofluorocarbons (CFCs) in inhaler devices approaches [1], the pharmaceutical industry has been involved with the production of CFC-free delivery devices. These include both dry powder inhalers (DPIs) and metered-dose inhalers (MDIs) using non-CFC propellants. The aim of the present study was to compare the delivery of salbutamol from the Turbuhaler® DPI, shown to be one of the most efficient DPIs available [2–5], and a CFC-free MDI used with a novel small volume metal spacer (NebuChamber®). The NebuChamber® is a 250 mL antistatic spacer device, which has been demonstrated to reduce the problem of static charge, which can affect large volume plastic spacers [6, 7]. Static charge has been demonstrated to be a problem, in that it can affect the drug delivery both of corticosteroids and salbutamol inhaled *via* small and large volume plastic spacers [7–10].

We have previously demonstrated that the pharmacokinetic profile of salbutamol in the first 20 min after inhalation represents the bioavailability from the lung but not the gastro-intestinal tract, with the latter moiety contributing 0.3% to the overall systemic bioavailability from an inhaled dose [11, 12]. This method of measuring lung bioavailability of salbutamol can, therefore, be applied to compare the lung deposition from different inhaler devices [13–15].

It is also worth noting that both of these inhaler devices overcome the problem of poor inhaler technique, which is recognized as a common problem with asthmatics, particularly when using standard MDIs. We were, therefore, interested in establishing whether significant differences exist *in vivo* in terms of lung delivery of salbutamol given by DPI (Turbuhaler®) and by a small volume antistatic metal spacer (NebuChamber®).

### Materials and methods

Ten healthy volunteers, mean (SEM) age 21 (0.7) yrs, forced expiratory volume in one second (FEV<sub>1</sub>) 105 (3)% of predicted, were studied in a randomized, single (investigator)-blind, cross-over design. Single doses of 1,200 µg salbutamol from Inspieryl Turbuhaler® (Astra Draco, Lund, Sweden) and Airomir® MDI (3M Healthcare Ltd, Loughborough, UK) *via* a NebuChamber® without mask (Astra Draco, Lund, Sweden) were given as 12 sequential 100 µg inhalations over 6 min. Mouth rinsing was performed after every inhalation to further obviate the possibility of a small amount of gastro-intestinal absorption.

The subjects were studied on 2 days separated by 1 week. They were carefully instructed in inhalation technique, as described by the manufacturers' literature. A

Turbuhaler® training device (Astra Draco, Sweden) was used to ensure an optimal peak inspiratory flow rate of at least 60 L·min<sup>-1</sup>. The NebuChamber® was used for breathing from residual volume (RV) to total lung capacity (TLC), using single puffs with immediate inhalation from the spacer. Plasma salbutamol was measured at 5, 10, 15 and 20 min. Systemic  $\beta_2$ -responses were measured as plasma potassium, tremor and cardiac frequency (*fc*) taken at baseline, 5, 10, 15 and 20 min (all measurements made with the subject supine).

### Measurements

Finger tremor was measured using a previously validated method employing an accelerometer transducer (Entran, Ealing, UK) [16]. Cardiac frequency was measured from standard lead II of an electrocardiogram (ECG) monitor. Plasma potassium was assayed by flame photometry using an IL943 analyser (Instrumentation Laboratory Ltd, Warrington, UK). The intra-assay and interassay values for analytical imprecision were 0.41 and 1.04%, respectively.

Plasma salbutamol was assayed by high-performance liquid chromatography (HPLC), the extraction process using silica adsorption with chromatography followed by reverse phase ion pair HPLC and electrochemical detection. The analytical imprecision for plasma salbutamol was 7.8% (intra-assay) and 6.7% (interassay). The HPLC detection limit for salbutamol was 0.02 ng·mL<sup>-1</sup>.

Plasma concentrations were expressed as maximal ( $C_{max}$ ) and average ( $C_{av}$ ) values over the 5, 10, 15 and 20 min time-points.

### Statistical analysis

The results were analysed using the "statgraphics" statistical software package (STSC Software Publishing Group, Rockville, USA). For all parameters, comparisons were made by multifactorial analysis of variance (MANOVA). A p-value of less than 0.05 (two-tailed) was considered significant.

### Results

Significant differences were found between the NebuChamber® and the Turbuhaler® for salbutamol  $C_{max}$  and  $C_{av}$  as shown in figure 1 and table 1. The NebuChamber® produced significantly ( $p < 0.001$ ) higher salbutamol levels:  $C_{max}$  N 6.80 vs T 3.76 ng·mL<sup>-1</sup> (95% CI for difference 2.41–3.66 ng·mL<sup>-1</sup>);  $C_{av}$  N 5.82 vs T 3.44 ng·mL<sup>-1</sup> (95% CI for difference 1.50–3.26 ng·mL<sup>-1</sup>). There was a 1.89 fold difference (95% CI 1.56–2.22) between these devices for  $C_{max}$ , and a 1.78 fold difference (95% CI 1.42–2.15) for  $C_{av}$ . Individual data for  $C_{max}$  are presented in figure 2, and show only one overlapping value between the two devices. There were no significant differences between the devices in terms of time to maximal concentration ( $T_{max}$ ) for salbutamol.

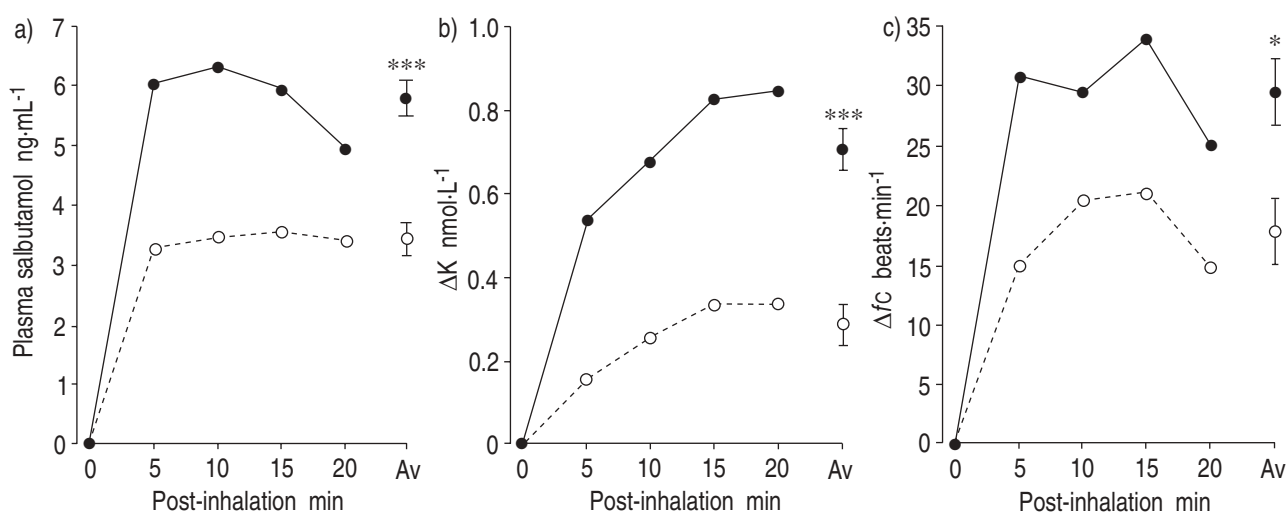


Fig. 1. — a) The mean plasma salbutamol concentration; b) the decrease in plasma potassium ( $\Delta K$ ); and c) the increase in cardiac frequency ( $\Delta fc$ ), at 5, 10, 15 and 20 min after inhalation of salbutamol. The average (Av) for all time-points is also shown with SEM. \*:  $p < 0.05$ ; \*\*\*:  $p < 0.001$ , significant difference between NebuChamber® and Turbuhaler®. —●—: NebuChamber®; —○—: Turbuhaler®.

Table 1. — Average and maximal values for plasma salbutamol level, fall in plasma potassium ( $\Delta K$ ) level, increase in cardiac frequency ( $fc$ ), and  $T_{max}$  values for each parameter

		Salbutamol	$\Delta K$	$\Delta fc$
Average <sup>‡</sup>	NebuChamber®	5.82 (1.50–3.26)*	0.71 (0.25–0.60)*	29.6 (2.8–20.5)*
	Turbuhaler®	3.44	0.29	17.9
Maximum <sup>‡</sup>	NebuChamber®	6.80 (2.41–3.66)*	0.86 (0.32–0.67)*	40.5 (1.7–27.3)*
	Turbuhaler®	3.76	0.37	26.0
$T_{max}$ <sup>#</sup>	NebuChamber®	10 (5–15)	20 (10–20)	10 (5–20)
	Turbuhaler®	10 (5–20)	20 (10–20)	10 (5–15)

<sup>‡</sup>: mean value, and 95% confidence interval for the difference between treatments in parenthesis; <sup>#</sup>: median, and range in parenthesis. \*:  $p < 0.05$ , significant difference between treatments.  $T_{max}$ : time to maximal concentration/response.

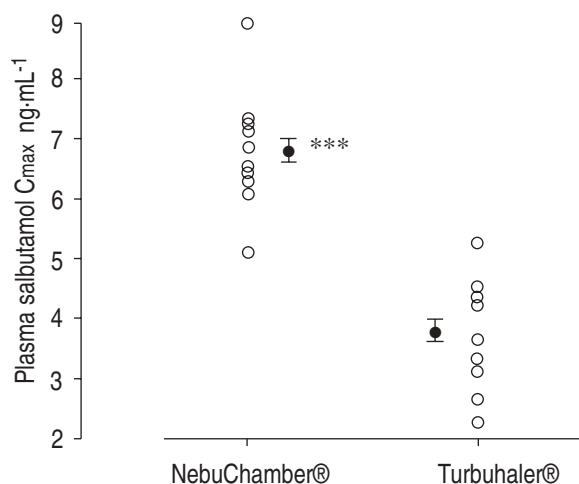


Fig. 2. — Individual values for maximal plasma salbutamol concentration ( $C_{max}$ ), comparing the NebuChamber® and Turbuhaler®. Mean values (●) and SEM are also presented. \*\*\*:  $p < 0.001$ , for comparison between the devices.

Differences were also found with systemic  $\beta_2$ -responses, in keeping with the pharmacokinetic data (table 1). These differences were highly significant both for cardiac frequency and plasma potassium, as shown in figure 1. For tremor the same trend was seen; however, the differences were not significant (log units for average), NebuChamber® (0.68), Turbuhaler® (0.49).

## Discussion

We found that, *in vivo*, delivery of non-CFC salbutamol aerosol *via* a small volume metal spacer (NebuChamber®) was significantly greater than salbutamol *via* an efficient DPI (Turbuhaler®). This amounted to almost a twofold difference in salbutamol bioavailability between these devices, which was also mirrored by dynamic responses. The use of the 20 min plasma salbutamol profile reflects absorption from the lung but not from the gastro-intestinal tract, with the latter contributing only 0.3% to the overall bioavailability when given by the inhaled route. However, it is unclear what proportion of this absorption originates from alveolar or bronchial sites.

It is important to determine whether differences in lung deposition of salbutamol are likely to result in commensurate improvements in bronchodilator response. For most patients with stable asthma, 200  $\mu\text{g}$  of salbutamol will result in a bronchodilator response approaching the top of the dose-response curve. However, in more severely affected patients or during an acute attack, much higher doses are required to optimize the bronchodilator response on the steep part of the curve [17]. In a study of patients with moderately severe asthma comparing two nebulizers with different respirable dose outputs, it was shown that an increase in lung bioavailability of salbutamol was associated with an improved bronchodilator response [18]. In the setting of acute severe asthma, it is, therefore, possible that an improved bronchodilator response may be achieved with better lung deposition, although this factor can be obviated simply by administering a greater number of puffs to achieve the same response.

An important point to make regarding the present results is that they relate only to salbutamol in these specific inhaler devices. The Turbuhaler® is accepted as an efficient inhaler device, with similar figures for radio-labelled deposition both for the corticosteroid, budesonide, and the  $\beta_2$ -agonist, terbutaline [3]. However, it may be the case that salbutamol lung deposition from the Turbuhaler® is not as great as for terbutaline or budesonide, although we are not aware of any such comparative data.

It is also possible that the results seen with the NebuChamber® may reflect the use of a non-CFC salbutamol MDI formulation, and that comparable deposition would not be achieved with a CFC formulation. It is also worth pointing out that in everyday clinical practice, effects of static charge will have minimal impact with the metal NebuChamber®, in terms of obviating effects of multiple puffs or inhalation delay [7]. Hence, it is likely that the results of our study using single puffs without delay will be equally applicable to what happens in real life.

In conclusion, plasma salbutamol pharmacokinetic measurement for determining lung bioavailability provides a sensitive method for comparing deposition of inhaler devices *in vivo*. In this study, salbutamol from a chlorofluorocarbon-free salbutamol metered-dose inhaler *via* the NebuChamber® produced significantly greater lung bioavailability than salbutamol from a dry powder inhaler, Turbuhaler®.

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