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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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 (Cmax) and average (Cav) value.

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

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®).

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 (FEV1) 105 (3)% of predicted, were studied in a randomized, single (investigator)-blind, cross-over design. Single doses of 1,200 µg salbutamol from Inspiryl 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⁻¹. 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 β2-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⁻¹.

Plasma concentrations were expressed as maximal (Cmax) and average (Cav) 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 Cmax and Cav as shown in figure 1 and table 1. The NebuChamber® produced significantly (p<0.001) higher salbutamol levels: Cmax N 6.80 vs T 3.76 ng·mL⁻¹ (95% CI for difference 2.41–3.66 ng·mL⁻¹); Cav N 5.82 vs T 3.44 ng·mL⁻¹ (95% CI for difference 1.50–3.26 ng·mL⁻¹). There was a 1.89 fold difference (95% CI 1.56–2.22) between these devices for Cmax, and a 1.78 fold difference (95% CI 1.42–2.15) for Cav. Individual data for Cmax 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 (Tmax) for salbutamol.

Plasma concentrations were expressed as maximal (Cmax) and average (Cav) values over the 5, 10, 15 and 20 min time-points.
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 µg 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 β₂-agonist, terbutaline [3]. However, it may be the case that salbutamol lung deposition from the Turbuhaler® is not as great as for salbutamol or terbutaline, 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®.

References


