The importance of the device in asthma therapy

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Abstract Inhalation is the preferred route for drug delivery in asthma treatment. Successful management of asthma depends on achieving adequate delivery of inhaled drug to the lungs, and to this end the role of the device used for delivery is very important. Aerosolized anti-asthma medications have been available for more than 40 years as pressurized metered dose inhalers (pMDIs), but more recently dry powder inhalers (DPIs) have been developed as an alternative. Laboratory assessment of fine particle dose has been shown to correlate to pulmonary deposition if the assessments are performed with an in vivo-like set up. The DPI Turbuhaler® delivers a high proportion of the dose as fine particles suggesting high pulmonary deposition. This finding has been confirmed by lung deposition studies, which indicate superior pulmonary deposition from Turbuhaler compared with a pMDI. This superior delivery to the lungs with Turbuhaler is reflected in a better clinical effect, as measured by greater improvements in lung function. The DPIs such as Turbuhaler are easy to use, and Turbuhaler has been shown to function well in a constrained situation such as an acute asthmatic exacerbation. Furthermore, the use of Turbuhaler in acute asthma will provide rapid clinical improvement. The in vivo variability in lung deposition obtained with Turbuhaler is lower than with pMDI, indicating that the performance of Turbuhaler is less dependent on patient competence. Thus, the development of Turbuhaler represents an important step forward in the effective management of asthma.

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INTRODUCTION

Asthma is a disease for which inhaled treatment is generally preferred to systemic or oral treatment. Successful management of asthma depends on achieving adequate delivery of inhaled drug to the lungs, and the role of the inhalation device is of major importance. Aerosolized asthma medications have been available for more than 40 years as pressurized metered dose inhalers (pMDIs), but there is increasing evidence to show that a large proportion of asthmatic patients do not benefit fully from their drugs because of poor inhaler technique (1). Moreover, the propellants used to generate the aerosol are often chlorofluorocarbons, which are thought to deplete the ozone layer and are to be phased out of production (2). Consequently, pharmaceutical companies have focused their attentions on the development of alternative inhaler systems. In this context, dry powder inhalers (DPIs) have been proposed as a valuable alternative (2).

This paper discusses the effectiveness of inhalers, in particular the DPI Turbuhaler®, with regard to lung deposition and elicited effects. The value of in vitro methods for predicting lung deposition, as well as variability in inhaler performance, will also be discussed.

THE VALUE OF IN VITRO STUDIES FOR PREDICTING CLINICAL OUTCOMES

Pulmonary deposition of inhaled drugs is influenced by the size distribution of the inhaled particles. Fine particles, defined as those of less than 5 μm in aerodynamic diameter, are more likely to reach the lower airways than larger particles. Characterization of aerosol formulations in the laboratory is important in guiding pharmaceutical product development and is used in final quality control. If the analytical set-up is modified, in vitro analysis can be used to predict lung deposition of the inhaled formulation.

Traditionally, the cascade impactor has been used to classify the particle size distribution of an aerosol in vitro. If the common glass bulb impactor inlet is exchanged for an anatomically correct cast of a human throat, the results show a good correlation with lung deposition data. Measurements of lung deposition can be made in vivo, using, for example, the charcoal-block method (3).

Using the described in vitro and in vivo methods, the in vitro fine particle dose and the in vivo lung deposition of salbutamol was compared for three DPIs (Turbuhaler®, Rotahaler® and Cyclohaler®) and a pMDI (4). Both in vitro methods numerically overestimated the amount of...
lungs deposition, although the anatomical throat replica resulted in a better correlation with the observed level of lung deposition in humans. More importantly, using the adult throat replica as the impactor inlet allows better comparison of the pMDI data with the DPI results than using the glass bulb. This suggests that in humans, interaction of the throat with an aerosol cloud from a pMDI is stronger than with an aerosol cloud from a DPI. An aerosol cloud from a DPI is a stable aerosol while that from a pMDI is dynamic and changing. A plot of lung deposition against fine particle dose, obtained using the anatomical throat replica, shows good correlation (Fig. 1). This suggests that the use of an anatomically accurate throat as the inlet to the cascade impactor may be a step forward in the attempt to bridge the in vitro model data with lung deposition.

**LUNG DEPOSITION AND CLINICAL EFFECT**

The development of new inhalation devices has highlighted the issue of the relationship between pulmonary deposition and therapeutic effect of inhaled drugs in patients with obstructive lung disease. The importance of pulmonary deposition for therapeutic effect has been examined in a study comparing administration of the β2-agonist terbutaline via Turbuhaler and pMDI (5). Pulmonary deposition with Turbuhaler was about 20%, double that achieved with the pMDI (Fig. 2). This increased deposition with Turbuhaler was reflected in a superior clinical effect, as measured by greater improvements in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow (FEF) at 25%, 50% and 75% of FVC (FEF25, FEF50, FEF75, respectively) and peak expiratory flow rate. This suggests that Turbuhaler is the preferred device for inhalation of asthma drugs when compared with a pMDI.

A recent study has compared fine particle dose and lung deposition of formoterol delivered by Turbuhaler or Aerolizer® in healthy subjects (6). Both devices showed a good correlation between fine particle dose and lung deposition. However, lung deposition was consistently higher with Turbuhaler compared with Aerolizer; on average, 41% more formoterol was deposited in the lungs with Turbuhaler.

A clinical study compared the bronchodilatory effect of formoterol at doses of 9 μg administered via Turbuhaler or 12 μg administered via Aerolizer (7). While there was a trend for greater therapeutic effect when the drug was administered via Turbuhaler, the differences were not significant. Possible explanations for the absence of significance could be that too few patients were included in the study (n=19), or that the doses used were at the upper end of the dose-response curve. Comparisons should ideally be performed using more than one dose from at least one of the devices being compared; this makes it possible to verify that the doses used were on the steep part of the response curve.

The relationship between the site of deposition of a drug in the lung and clinical effect is poorly understood. More is known about where inhaled drugs are actually deposited than where they should ideally be deposited. It is virtually impossible to achieve peripheral deposition without some deposition in central areas. While the proportion of peripheral to central deposition can be

![Figure 1.](image1.png) Correlation between lung deposition of salbutamol and the fine particle dose obtained using the anatomical throat replica as inlet to the cascade impactor (4). Two points are shown for each DPI, representing moderate and weak inhalation efforts. TH: Turbuhaler; RH: Rotahaler; CH: Cyclohaler; pMDI: pressurized metered dose inhaler. Mean ± SEM. [Reproduced with permission from Interpharm Press Inc.]

![Figure 2.](image2.png) Lung deposition after inhalation of 0.25 and 0.5 mg of terbutaline sulphate either via pressurized metered dose inhaler (pMDI) or via Turbuhaler (TH). Pulmonary deposition (mean ± SD) is expressed as a percentage of the nominal dose (5). [Reproduced with permission from Am J Respir Crit Care Med.]
determined for different inhalation systems, there is little evidence to indicate which is more beneficial in terms of clinical effect.

**TURBUHALER IN ACUTE ASTHMA**

The efficacy of drug delivery with Turbuhaler is an important issue for the as-needed use of Oxis® Turbuhaler® in acute asthma. For all DPIs, a higher peak inspiratory flow rate will result in more efficient drug delivery, and there have been concerns that patients suffering from acute asthma exacerbations would not be able to use a DPI in the acute asthma situation. However, a study in 99 patients with acute asthma exacerbations (mean FEV₁ = 1.21) found that the mean flow through Turbuhaler in this group of patients was 60 l/min, with all but 2 patients in the study achieving flow rates above 30 l/min (8). These data are very similar to those obtained in a mild asthmatic population (9). A similar study in acute asthma patients found that all patients except one (n = 43) could generate a peak inhalation flow rate through Turbuhaler greater than 30 l/min, and the therapeutic effect (measured by increase in FEV₁ after 10 min) was only weakly correlated with the inhalation flow rate (10). Hence, both of these studies indicate that Turbuhaler is a suitable device for as-needed therapy in acute asthma.

The peak inhalation flows obtained are consistent with the clinical results of a study in patients with severe acute airway obstruction (mean FEV₁ = 0.91) who, on admission to hospital, received 2.5 mg terbutaline via Turbuhaler or pMDI with spacer, followed by a second dose after 15 min (11). The improvement in FEV₁ after 25 min was significantly greater (P = 0.0004) with Turbuhaler than with pMDI plus spacer (Fig. 3). The study by Nana et al. (10) also investigated the efficacy of salbutamol, delivered via Turbuhaler or pMDI, in 86 patients with acute asthma. Salbutamol was given via Turbuhaler at 0, 15, 30 and 45 min at doses of 100, 300, 300 and 300 µg, respectively, and the regimen was repeated at 90, 105, 120 and 135 min, giving a total dose of 2000 µg. The same schedule, with double doses, was used with the salbutamol pMDI, giving a total dose of 4000 µg. Similar improvements in FEV₁ were observed with both treatments over the study period of 165 min. Taken together, these studies confirm that Turbuhaler can be used effectively in patients with acute asthma, providing rapid clinical improvement.

**VARIABILITY IN DRUG DELIVERY AND THE EFFECT OF PATIENT-RELATED FACTORS**

Variability in drug delivery is an important consideration for inhalation therapy, and both device- and patient-related factors can potentially influence this variability.

For DPIs, the respirable fraction obtained will depend, to a certain extent, on the inhalation flow rate through the device. While it is generally assumed that Turbuhaler has a larger flow-dependence than other devices such as Diskus®, a low inhalation flow rate through Turbuhaler will result in a similar respirable fraction to that obtained with a normal flow through Diskus; consequently, a normal flow through Turbuhaler will result in a higher fine particle dose to the lungs.

The flow resistance of a device can also affect the variability of drug delivery. Studies have shown that inhaling against some resistance results in higher and more reproducible drug delivery than inhaling against no resistance (12), although the resistance that results in optimal delivery is unknown.

There have been concerns that devices such as Turbuhaler are sensitive to humidity, although a study in Australia has demonstrated that Turbuhaler can be used effectively in humid conditions (13). Turbuhaler is one of the few devices to have a protective cap, and proper use of this cap should ensure humidity does not affect the performance of the device.

Studies in healthy volunteers have shown that variability in drug delivery is markedly lower with Turbuhaler than with a pMDI (14). Both intra- and intersubject variability are reduced with Turbuhaler compared with a pMDI (47% vs. 73% and 19% vs. 47%, respectively). Intersubject variability is also reduced with Turbuhaler compared with pMDI in asthma patients (14). These data indicate that the performance of Turbuhaler is less dependent on the individual subject compared with the performance of a pMDI, and that Turbuhaler gives a more reproducible dose to the lungs than the corresponding pMDI.

By contrast, variability in vitro has been shown to be higher with Turbuhaler (14). This disparity is probably due to the fact that in vitro variability accounts for only a small part of the overall in vivo variability in the clinical
situation—patient-related factors also impact on the variability of inhaler performance (14).

Patient competence is a problem that is particularly pertinent to aerosol therapy, and it has been shown that many patients experience problems in using their inhaler correctly (15). This is particularly true of pMDIs, which are subject to a number of difficulties. These include the need to coordinate inhalation and actuation, and the cold freon effect; impaction of the aerosol jet on the back of the throat results in a gag reflex and minimal drug deposition in the airway. Compliance is a major issue with all types of therapy; although non-compliance with inhaled therapy is known to be common (16), predicting which patients are likely to be non-compliant is impossible. A third patient-related factor is contrivance; even with adequate tuition, patients will often not use their inhalers as instructed.

Of the patient-related factors that impact on the variability of inhaler performance, competence is perhaps the most amenable to elimination by improvements in the delivery device. The generation of an aerosol and its inhalation is a continuous process with Turbuhaler and other breath-actuated DPIs, in contrast to pMDIs where the two processes are distinct and require coordination by the inhaling patient. This functional difference may explain why lung deposition is more predictable when using Turbuhaler compared with a pMDI (14).

CONCLUSIONS

The clinical effect of an asthma drug relies on its pulmonary deposition, which in turn is dependent on the fine particle dose of the generated aerosol. In vitro data show a better correlation with in vivo data if an anatomically accurate replica human throat is used as an inlet to the impactor.

Effective management of asthmatic patients relies on achieving adequate delivery of inhaled drugs to the lungs. Several factors can influence pulmonary deposition, including the performance of the delivery device itself and patient handling. Turbuhaler has been shown to deliver a more reproducible dose than a pMDI, suggesting that the performance of Turbuhaler is less dependent on the patient compared with a pMDI. In addition to providing a more reproducible dose than a pMDI, Turbuhaler has been shown to provide superior lung deposition, leading to a superior clinical effect. Especially, Turbuhaler has been shown to deliver more drug to the lungs compared with Aerolizer. Concerns regarding the use of DPIs such as Turbuhaler in acute asthma would appear to be unfounded, with several studies demonstrating that Turbuhaler provides rapid clinical improvement when used for as-needed therapy in acute exacerbations. Thus, Turbuhaler provides several improvements over alternative delivery devices for the effective management of asthma.

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