Expert Opinion

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Controlled inhalation of aerosolised therapeutics

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With the advent of new, and often expensive, therapeutics designed for aerosol delivery to the lung, there is a need to improve the targeting and efficiency of their delivery. By controlling breathing patterns associated with inhaled aerosols, it has been shown that deposition in the lung can be both maximised and targeted to specific lung regions. A new commercially available device, the AKITA (Inamed GmbH) allows for individualised, controlled inhalation of aerosols produced by conventional nebulisers. Smart card technology is incorporated into the AKITA to both individualise breathing patterns as well as record compliance of therapy. So far, the use of this new device has provided maximal delivery of drug to the lung, with improved patient compliance and minimal waste of drug.

Keywords: aerosol delivery, aerosol deposition, breathing patterns

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1. Introduction

Aerosolised therapeutics are commonly used to treat or prevent a variety of lung diseases [1]. Furthermore, the lung has recently been considered as the portal of entry for a number of aerosolised drugs designed to act systemically (e.g., insulin, growth hormone, IFN-β and calcitonin) [2]. In either case it may be desirable to both optimise total deposition and target delivery of these aerosolised drugs to specific regions of the lung. The general rationale for targeting aerosol delivery to specific regions of the lung is to maximise the drug effect to the region desired whilst minimising unwanted side effects to other regions. For example, there has recently been interest in precise targeting of cytotoxic drugs to the lungs for treating lung cancer in a manner that will minimise systemic toxicity [3]. An additional reason for maximising total deposition and targeting drugs to their desired location is to improve the cost effectiveness of drug delivery (e.g., expensive and limited availability of α_1-antitrypsin [4]). Finally, it is also desirable to reduce patient inhalation times in order to improve compliance. Consequently, new aerosol delivery technologies are currently being developed to meet these goals of improved targeting, reduced waste and improved patient compliance.

Total or whole lung aerosol deposition refers to the fraction of inhaled particles deposited in the lung on a breath-by-breath basis. Regional deposition of aerosol, in its simplest sense, can be thought of as differentially partitioning drug delivery between the conducting airways and the alveolar region of the lung. But regional deposition may also be considered in terms of deposition between parallel compartments of the lung (e.g., an apical, middle and basal compartments) [5]. It has been recognised for some time that manipulation of breathing patterns can affect both total and regional deposition in the lung [6-8]. Slower breathing increases total deposition in the lung by time-dependent mechanisms (i.e., sedimentation for particles in the 1 – 5 µm aerodynamic diameter size range). Increasing tidal volumes tend to increase deposition by bringing a larger fraction of the aerosol to the smallest airspaces. Finally, flow rate also affects particle deposition by velocity-dependent mechanisms (i.e., inertial impaction, especially for

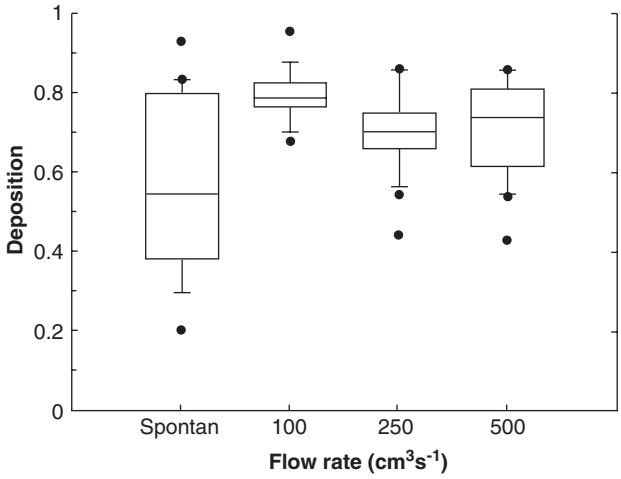

Figure 1. Fractional lung deposition of monodisperse 3 m MMAD aerosol in COPD patients for spontaneous (spontan) versus controlled breathing. BRAND P, FRIEMEL I, MEYER T, SCHULZ J, HAUSSINGER K: Total deposition of therapeutic particles during spontaneous and controlled inhalations. *J. Pharm. Sci.* (2000) **89**:724-731 [13]. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.
COPD: Chronic obstructive pulmonary disease; MMAD: Mass median aerodynamic diameter.

particles > 3 µm aerodynamic diameter). Increasing inspiratory and expiratory flow rate enhances particle deposition in the large airways of the lung where air velocities are highest. Current studies also show that uneven regional ventilation in cystic fibrosis (CF) patients has variable effects on pulmonary and airway deposition in these patients (i.e., enhanced pulmonary deposition in well-ventilated regions but enhanced bronchial airways deposition in poorly ventilated regions [9,10]). Further modelling of these ventilation patterns in the CF lung suggests that breathing patterns may be optimised to improve deposition to the compromised, small airways of these patients [11].

Given the importance of breathing patterns in inhaled particle deposition, it may not be surprising that the variance in total and regional particle deposition of inhaled particles has been shown to be reduced by controlling/standardising breathing patterns [6,12-14]. Using monodisperse particles of similar mean size to that of a Pari LC Star® jet nebuliser (3 µm), Brand *et al.* [13] recently showed that total respiratory tract deposition for spontaneous breathing patterns varied from 20 to 95% in patients with pulmonary disease (chronic obstructive pulmonary disease [COPD] and asthma). They were able to show decreased intersubject variability and an increase in total deposition (i.e., deposition in the entire respiratory tract) for controlled breathing patterns compared with the spontaneous breathing condition associated with breathing on a nebuliser (**Figure 1**). For the low-flow condition (100 ml/s), with the least variability in total deposition, there was no correlation between lung function (varying from 30 to 130% pred forced expiratory volume for 1 s) and deposition fraction. This low-flow, large tidal volume condition also enhanced the efficiency of delivery by both increasing the residence time of aerosol in the lung and bringing more of the aerosol to the deep lung regions with the smallest airspaces. To control breathing patterns in this study Brand *et al.* [13] used a piston-type ventilator and computer-controlled valves such that when subjects tried to inhale at the mouthpiece a negative pressure initiated the ventilator that then filled the lungs with the aerosol at a preselected tidal volume and flow. At the end of inhalation, the ventilator reversed direction and the subject exhaled at the prescribed flow rate. During the entire breathing cycle, deposition was determined by light scattering photometry at the mouthpiece.

There are certainly other factors that determine efficiency of aerosol delivery to a patient's lungs, including the particle size distribution of the aerosol and the specific morphology of the individual's lung. The latter cannot be controlled but the choice of aerosol delivery device (e.g., nebuliser) can determine a wide range of particle sizes. Thus, by combining the appropriate aerosol delivery device with technologies designed for controlling inhaled volumes and flowrates, inhaled aerosols may be more efficiently and reproducibly targeted to the regions of the lung most affected by lung disease.

2. AKITA technology

Subsequent to the Brand *et al.* study [13], Inamed GmbH developed the AKITA, a commercially available device that allows individualised, controlled inhalations in combination with conventional nebulisers (**Figure 2**) [4]. Using an individual smart card for each patient the inhalation flow rate, inhaled volume and a breath-holding period can be precisely predetermined based on the subject's lung volume. The AKITA device also allows for pulsing of the aerosol at any period of the inspiration (e.g., either permitting the inspiration phase to be terminated with an aerosol-free interval so as to avoid useless drug deposition in the dead space of the lung, or introducing the aerosol in a small bolus at the end of inspiration to target the larger airways). The optimised breathing pattern of the patient is stored on the smart card, which, similar to a phone card, is slid into the AKITA device before the first inhalation. A compressor in the AKITA device both delivers the predetermined flow rate of aerosol to the lung through the nebuliser with each inhalation, while also providing the pressure to drive the jet nebuliser. After the patient has actuated the device with a slight inspiratory effort on the nebuliser mouthpiece, the AKITA takes over control of the inhalation, ventilating the lung with small positive pressure at a constant flow rate, while giving the patient a display feedback on the time remaining for each breath and the number of breaths remaining for the prescribed dose. Compliance data (i.e., actual inhaled volumes/flows and number of breaths) are also recorded on the smart card for subsequent analysis.

Figure 2. AKITA (Inamed GmbH): the first inhalation system that controls compliance and medication dose. Here shown with the Pari LC Star® nebuliser.

3. Clinical application of the AKITA technology

Using this new commercial device, Brand *et al.* [4] showed an advantage in time and delivered dose of α_1-protease inhibitor (Prolastin®; Bayer) to the parenchyma of the lung in COPD patients, compared with both spontaneously breathing with the nebuliser alone (Pari LC Star) and with the Halolite 'adaptive aerosol delivery' device [15]. This latter computer-controlled device is also designed to decrease variability in dosing of therapeutic aerosols to the lungs of patients. But in the case of the Halolite, pulses of aerosols are delivered into each inspiration by monitoring the flow characteristics of each breath in the patient's spontaneous breathing pattern. Once the trend of the patient's breathing pattern has been established in the first three breaths, the start of each subsequent breath is identified rapidly and accurately, allowing aerosol to be pulsed into the very beginning of each inspiration, ensuring maximum opportunity for the aerosol bolus to penetrate deep into the lung [15]. However, unlike the AKITA, the breath volume and period itself is not controlled (i.e., patients still breathe spontaneously). For this comparative study [4] the controlled breathing pattern for the AKITA, derived from *in vivo* deposition studies [16], was a flow rate of 200 ml/s and a tidal volume of 0.8 l of the subject's inspiratory capacity (average 1.75 l). The authors found that the time required to deposit the necessary 50-mg dose of Prolastin in the lungs of patients was shortest for the AKITA system (18 – 24 min) compared with the Halolite (100 min) and the Pari LC Star alone (44 min). Subsequent to these preliminary comparisons, the AKITA system has now been successfully used with the Pari LC Star nebuliser for delivery of α_1-antiprotease therapy in patients with this deficiency.

In a more recent study [17], the AKITA was used to deliver glutathione aerosol for therapeutic purposes in patients with CF over a 2-week period to assess the effect of the therapy on oxidant status in subsequent bronchoalveolar lavages (BALs). Intrathoracic deposition with the AKITA was 86.3 ± 1.4% of the emitted dose. The time needed to complete nebulisation of the targeted dose with glutathione 300 or 450 mg was 18 ± 1 min. As a result, glutathione concentrations in BAL fluid were increased three- to fourfold 1 h after inhalation and at 12 h were still almost doubled. Although the increase in BAL glutathione levels did not produce changes in BAL fluid content of oxidised proteins and lipids, the ability of the AKITA to dramatically and consistently increase glutathione levels provided further validation of the technology.

In the two applications of the AKITA discussed in this section, the goal was to optimise total deposition to the peripheral, pulmonary airspaces, the therapeutic target for these drugs. There are also therapeutic applications that require targeting of drug delivery to the bronchial airways. For example, recent developments of viral and liposomal vectors for DNA transfer to airway epithelial cells in CF will require targeted delivery to the bronchial airways where the defect in epithelial Cl^- transport (CF transmembrane conductance regulator) is manifested [18]. Deposition of these vectors in the lung periphery, besides being ineffective in this region, may also enhance an innate immune response to the deposited therapy. In addition, it is likely that cost factors will also dictate optimal delivery to the airways for these vectors. The AKITA device can also be programmed to optimise delivery to the bronchial airways of the lung by varying inhaled flow rate and pulsing the aerosol at shallow inhalation depths. This latter capability provided by the AKITA is similar to that provided by the Halolite technology [15]. For the case of targeting the bronchial airways,

however, the nebuliser is pulsed towards the end of inhalation. Although this application of the AKITA has not been applied to any inhaled therapeutics so far, the feasibility of such targeting with shallow aerosol boli has been validated by a number of investigators [19-21]. Another method that has recently been employed to deliver particles to the bronchial airways is the extremely slow inhalation technique described by Anderson *et al.* [22]. These investigators instructed subjects to inhale large particles, mass median aerodynamic diameter 6 µm, with very low inhalation flow rates (0.04 l/s), conditions under which they predicted that these large particles would settle out in the small bronchial airways before reaching the alveolar region. The subsequent clearance kinetics for these inhaled, deposited particles supported this contention (i.e., a slow but significant clearance of particles from 24 to 96 h consistent with particle clearance from small airways). Again the AKITA provides the capability of controlling inhalation at very low flow rates to enable particle deposition in the small bronchiole airways. Such low inhalation flows would be difficult to ask patients to achieve on their own. In an attempt to find the optimal conditions for depositing particles in the bronchial airways of CF patients, Haeussermann *et al.* [23] found the highest bronchial deposition occurred with a small volume (0.5 l) of 5.5-µm particles inhaled at a low flow rate (100 ml/s). This study employed the same controlled, positive-pressure ventilation as the AKITA and was well tolerated by the CF patients, providing support for this targeting approach with the AKITA.

The evidence on patients' compliance and tolerance associated with AKITA use has so far been positive. In the inhaled glutathione study previously described, the assessed compliance was 86.5 ± 3.3% of the number of inhalation breaths that had to be taken during the 2-week period to inhale the targeted dose of glutathione. Some noncompliance occurred among almost all the CF patients, but only sporadically throughout the study period. To find evidence that controlled inhalations with AKITA are well tolerated by patients, especially those with airway obstructions, Meyer *et al.* [24] instructed asthmatics to use the AKITA for bronchodilator 'rescue' therapy following a bronchial provocation test. The patients were asked about the convenience of the AKITA controlled inhalation using a questionnaire. In 80% of patients the controlled inhalation was judged as convenient, neither as too slow nor fast, neither as too deep nor shallow. Thus, controlled deep and slow inhalations were found to be convenient and tolerable for patients with mild airway obstruction.

4. Expert opinion

Maximising dose and targeting specific areas of the diseased lung will become more desirable with the increasing use of aerosolised therapies. Currently, CF patients use a variety of nebulisers for daily therapies of recombinant human DNase (rhDNase), bronchodilators and antibiotics. Although recent use has been confined to the Pari LC Star and Pari LC Plus®, the AKITA could be adapted for use with most current jet and new vibrating mesh nebulisers. This may allow for more selective targeting by using different devices with a variety of particle size distributions (i.e., optimising both breathing conditions and particle size). Both rhDNase and tobramycin are approved for use with the Pari LC Plus nebuliser. One of the goals of aerosol therapy for CF patients is to reduce their time burden of taking multiple inhaled drugs. Use of the AKITA may help in this regard by providing more efficient delivery (i.e., requiring less time to deliver the same effective dose obtained under spontaneous breathing conditions). Although other new aerosol delivery devices may also achieve this goal of reduced therapy time [25-27], the unique ability of the AKITA to precisely control inhaled volumes and flow rates may further provide for the aerosol to be more efficiently and reproducibly targeted to the regions of the lung most affected by the disease.

Furthermore, the AKITA smart card technology will provide clinicians with valuable compliance data for each patient, allowing better care for patients. Although the AKITA is designed to provide for more precise dosing of nebulised aerosols to the lungs of patients, this goal should not be confused with an attempt to increase the dose over that which patients may receive when breathing spontaneously on a nebuliser. If patients are breathing as instructed by their physicians (e.g., slow, deep inhalations) they will receive a similar dose as provided by the AKITA under breathing conditions programmed by its smart card. The problem is that many patients do not breathe as instructed by their physicians and are likely to receive suboptimal doses of nebulised drug (as illustrated in **Figure 1**), especially when they are at home, away from the supervision of clinicians. Ensuring that patients use the AKITA technology, clinicians can be assured of better patient compliance.

With further understanding of the principles of aerosol deposition and lung physiology, investigators and clinicians may be able to target those areas of the lung where the drug can provide its maximum benefit and/or avoid those areas where maximum unwanted side effects may occur. Delivery of shallow aerosol boluses or inhalation of aerosols with extremely low flow rates may selectively target the bronchial airways of the lung, whereas large-volume inhalations and the use of breath-holds allow easy delivery of aerosol to the alveolar regions of the lung. Further mechanistic studies are needed to determine the optimal delivery conditions for targeting diseased regions of the lung affected by uneven ventilation. The AKITA technology currently provides the best state of the art tool for applying these targeting strategies in the clinical environment.

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