Expert Opinion

Challenges and opportunities in respiratory drug delivery devices

Kurt Nikander
Clinical Research and Development, Respiratory Drug Delivery, Philips Home Healthcare Solutions, Parsippany, NJ, USA

Recent reviews conclude that there is a need to improve the management of respiratory diseases treated with inhaled drugs, mainly asthma and chronic obstructive pulmonary disease (COPD). Healthcare professionals – mainly in primary care – seem to lack to some degree the evidence-based information required for the selection of the most appropriate respiratory drug delivery devices (inhalers) for the patients, whereas some of the patients often tend to have poor inhaler technique. This could have an impact on the ability to control the respiratory diseases in question. There are probably several reasons for these apparent challenges in the primary care arena. Owing to the abundance of inhalers available at present, especially for the treatment of asthma and COPD, it is quite a challenge to pick the 'right' inhaler for each patient. For an inhaler to be optimal, the patient has to be able to master the inhaler technique required for the specific inhaler. The patient–inhaler interfaces – mouthpieces or facemasks – can add important challenges that further diminish the efficacy of the treatment.

Keywords: dry powder inhalers, individualized inhalers, inhaler, inhaler technique, patient–inhaler interfaces, pressurized metered dose inhaler

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1. Introduction

The treatment of respiratory diseases with drugs delivered through different respiratory drug delivery devices (inhalers) has a history that dates back to the Ebers papyrus in Egypt ~ 1500 BC [1]. Throughout the early evolution of the inhalers, drugs available for treatment of the respiratory diseases seem to have been the drivers behind the development of inhalers such as pipes, straws, vaporizers and atomizers. The nebulizer emerged around the 1860s from the atomizer design by the addition of baffles to further break the crude spray into a respirable aerosol. The development of glass nebulizers with rubber bulbs made the nebulizers portable [2]. The portable nebulizer was replaced by the pressurized metered dose inhaler (pMDI) in the 1960s and 1970s with drugs such as isoprenaline, salbutamol and terbutaline.

The development of the new pMDI design was a good example of a 'challenge' with an 'opportunity'. Several surveys and clinical studies in the mid-1970s showed that a large proportion of patients had problems in coordinating inhalation with aerosol actuation [3,4]. An analysis of the ballistic nature of the pMDI aerosol showed that the speed of the aerosol declined over distance and approached the speed of a tidal inhalation between 5 and 10 cm from the pMDI mouthpiece [5,6]. To solve the problem pMDI 'add-on' devices such as the early tube spacer were designed to move the pMDI from the patient's mouth to the point where the speed of the aerosol matched the speed of the tidal inhalation (**Figure 1**). This was followed

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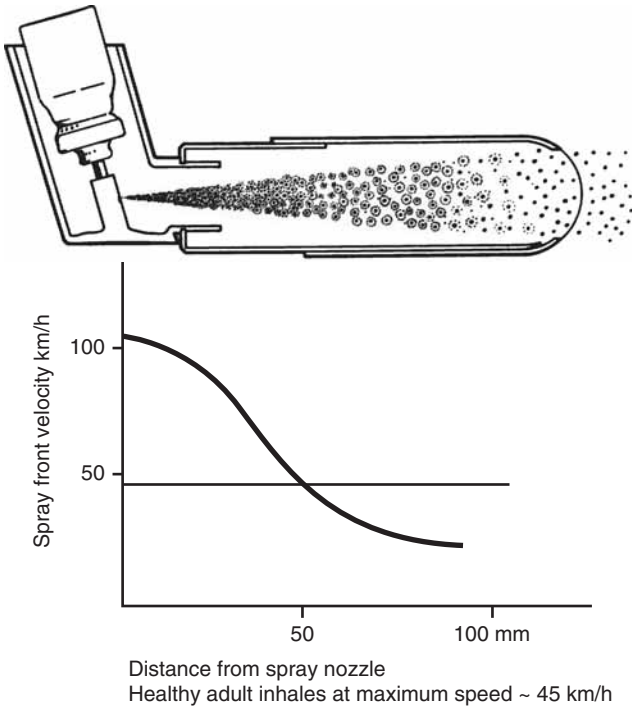

Figure 1. The tube spacer (Inhalet, Astra) from the late 1970s. The tube spacer was designed to move the pressurized metered dose inhaler from the patient's mouth to the point where the speed of the aerosol matched the speed of the patient's tidal inhalation. The maximal speed of the inhalation of a healthy adult was estimated to be ~ 45 km/h (line crossing the graph).

by other pMDI add-on devices such as conventional spacers and valved holding chambers (VHCs).

The main challenges facing healthcare professionals and patients today are not very different from those of the 1970s. How to choose the 'right' inhaler for the patient, how to improve the patient's inhaler technique, and the impact of patient–inhaler interfaces are still central aspects of the management of respiratory diseases.

2. Choosing the 'right' inhaler

There is a multitude of inhaler–drug combinations to choose from, especially in the treatment of asthma and chronic obstructive pulmonary disease (COPD). The prevalence for asthma has been reported to range from 1 to 18% of the population in different countries, whereas the prevalence for COPD has been reported to be ~ 6% [7,8]. This means that several hundreds of millions of patients with asthma and COPD rely on the efficacy of their inhalers. Data from the US show that between 28 and 68% of these patients cannot use their pMDIs and dry powder inhalers (DPIs) well enough to benefit from the treatment [9]. These numbers are even more depressing considering that 39 to 67% of the healthcare professionals who should be able to teach the patients to use the inhalers correctly do not seem to be able to perform that task properly [9]. The challenge is not minimized by the fact that a multitude of inhalers – pMDIs, DPIs, nebulizers – is available.

In a recent review the authors stated that > 100 inhaler–drug combinations for asthma are available, mainly pMDIs and DPIs [10]. If all the different nebulizer and compressor combinations were included, this number would be substantially higher. The number is, however, expected to increase with the introduction of generic inhaler–drug combinations. The challenge for healthcare professionals and pharmacists is obviously to select the 'right' inhaler–drug combination for each patient. Patient, drug and inhaler-related factors have to be considered in the choice of the right inhaler [11]. For example, if a patient is assigned one drug from a DPI and another from a pMDI, the confusion can get even worse. The 'right' inhaler would be one that the patient uses correctly with good adherence to the prescribed treatment regimen over time. Correct use would include proper cleaning and maintenance of the inhaler. Asthma management guidelines in general advocate pMDI VHC combinations for young children but tend to be rather unspecific regarding adults [10,12]. Patient preference has been advocated as a selection tool for the optimal inhaler, although there is scant evidence that patient preference would lead to correct use of the inhaler and reasonable adherence. In some countries with national healthcare systems the selection of inhaler–drug combinations is simplified by the insurance system, which reimburses only specific combinations. The request for a device to solve the problem with the multitude of inhaler–drug combinations was outlined recently as follows: 'We need a clinical tool to characterize a patient's inhalation pattern, check inhaler technique, and enable a match with an inhaler device; this tool should be inexpensive and easy to use' [13].

3. Inhaler technique

The development of new inhalers over the last few decades has brought a variety of pMDIs, DPIs, nebulizers and inhalers based on new technologies to the market. One of the main challenges for the manufacturers of the inhalers has been related to the training of the end users in their correct use. The instructions for using most of the inhalers seem to be confusing to both healthcare professionals and patients, as a large percentage of both groups seem to lack the skills required to use these inhalers correctly [14]. The available data show that in Europe up to 50% of patients with asthma or COPD lack the skills to use inhalers correctly, and up to 40% of children cannot use pMDIs with spacers or VHCs correctly [14]. One of the main challenges for the manufacturers of the inhalers has been related to the training of the end users in the correct use of the inhalers [15]. The incomplete therapeutic benefit could include too low or too high dosage of the drug, extrapulmonary deposition of the

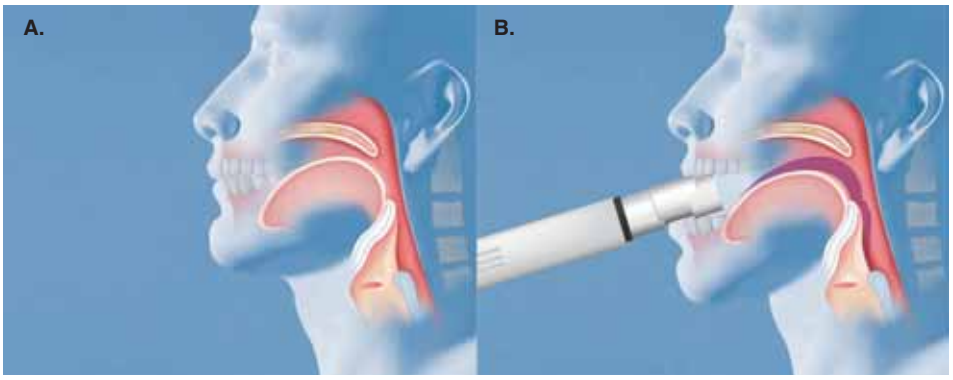

Figure 2. The figure shows an illustration of (A) the upper airways and (B) the same illustration with a stepped mouthpiece creating both vertical and horizontal mandibular advancements. The possible increase in the volume of the upper airways achieved through the mandibular advancements is highlighted by the purple shaded area.

aerosol leading to lack of therapeutic effect, and an increased rate of local side effects, for example in the oral cavity and the throat.

The mantra for how to get patients to use inhalers correctly has been and still seems to be 'training and more training' [14]. Modern healthcare is, however, notoriously short of time for patients when they visit primary care and hospitals. The challenge is therefore how to provide the patient with repeated instructions in the use of the inhaler with additional feedback on how the inhaler was used. Through built-in electronics, audio instructions could be added to inhalers to guide the patient at every step in the use of these devices. Intelligent inhalers such as the I-neb Adaptive Aerosol Delivery (AAD) System (Philips Respironics) already have built-in electronics that provide feedback, both directly and online, on how successfully the inhaler was used. These technologies could be built into pMDIs, pMDI add-on devices, DPIs and other inhalers to provide the patient with both user instructions and feedback. The relatively high unit cost associated with the provision of electronic feedback can be a problem at present, but in time the cost should drop with the availability of lower cost memory and related components.

4. Patient–inhaler interfaces

The patient–inhaler interface is usually either a mouthpiece or a facemask. The facemasks connected to pMDI VHCs have been shown to be of critical importance as any leakage of air can substantially reduce the amount of aerosol inhaled [16-18]. Unlike nebulizers, which generally have their own gas supply to transport the aerosol, once propellant expansion has taken place pMDIs offer no such transport. Therefore, inhalation through a leaky facemask-to-face seal will inevitably result in ambient air instead of aerosol being drawn into the facemask from the VHC, because the resistance of the leak is less than that of the most sensitive inhalation valve. Facemasks connected to nebulizers tend to leak aerosol around the top of the facemask with the possibility of aerosol deposition into the patient's eyes [19]. The challenge is to design new soft facemasks using facial anthropometric data to individualize the facemask in order to address these issues.

Change in vertical diameter of inhaler mouthpieces together with changes in peak inspiratory flows and particle sizes have been shown *in vitro* to affect the deposition efficiency of inhaled aerosol [20]. These results are likely to be important for future designs of inhaler mouthpieces. A prototype stepped mouthpiece designed to create mandibular advancements has been shown *in vivo* using acoustic pharyngometry to increase the size of the upper airways during inhalation (**Figure 2**) [21]. Acoustic pharyngometry has traditionally been used to evaluate the impact of various protrusive (vertical and horizontal) positions of the lower jaw achieved through oral appliances for patients with sleep apnea. The stepped mouthpiece design provided the tools for both vertical and horizontal movements (mandibular advancements) of the lower jaw. The incorporation of stepped mouthpieces in inhalers might be an important opportunity to increase the amount of aerosol deposited in the lungs through reduced upper airway deposition.

5. Expert opinion

It is rather surprising that despite the long history of inhalers, healthcare professionals and patients can still face so many challenges in the selection and use of these inhalers, especially the pMDIs and the DPIs. The relatively recent development of conventional add-on devices (spacers and VHCs), breath actuated pMDIs (example Autohaler, IVAX, Miami, FL, USA), reverse flow pMDI add-on devices (example InspirEase, Schering-Plough, Kenilworth, NJ, USA), breath coordinated pMDIs (example Optihaler, Philips Respironics, Parsippany, NJ, USA) and DPIs does not seem to have diminished the challenges [4,7,8].

The question is whether a focus on the patients' needs instead of the technological possibilities could be a way to partially solve these problems. It should be possible to create inhalers that are easy to use, easy to clean, with online feedback for both healthcare professionals and the patient, and with reminders to improve adherence. A future prospect would probably require the development of inhalers that could be individualized to match the development of personalized medicine. Individualized inhalers might enhance the patient's ability to use the inhaler correctly and would create the possibility for dose titrations to the lowest effective dose. This would profoundly change the present 'one size fits all' paradigm for most inhalers, but especially for the pMDIs and the DPIs.

The opportunities listed above could be quite challenging considering how time-consuming and therefore costly some of them might be. For example, the time limitations of primary caregivers could exclude them from receiving additional online feedback regarding their patients. To motivate any extra expenses for the implementation of some of the future opportunities, positive proof through clinical and health economics studies would be required.

Declaration of interest

The author is an employee of Philips Healthcare, Parsippany, NJ, USA.

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Affiliation

Kurt Nikander
Director,
Clinical Research and Development,
Respiratory Drug Delivery,
Philips Home Healthcare Solutions,
Parsippany, NJ 07054, USA
Tel: +1 978 594 0350;
E-mail: Kurt.nikander@philips.com