INHALER DEVICES: THE PAST, THE PRESENT, AND THE FUTURE

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Chairperson

Richard Dekhuijzen[1]

Speakers

Gary Wong,[2] J. Christian Virchow,[3] Henry Chrystyn[4-6]

1. Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen, Netherlands
2. Department of Paediatrics and School of Public Health, Chinese University of Hong Kong, Hong Kong
3. Department of Pneumology/Intensive Care Medicine, Medizinische Klinik 1, Zentrum für Innere Medizin, Universitätsmedizin Rostock, Rostock, Germany
4. Talmedica Ltd., St Crispin House, Haslingden, UK
5. Faculty of Health and Human Sciences, University of Plymouth, Plymouth, UK
6. Research in Real Life (RiRL), Cambridge, UK

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MEETING SUMMARY

Inhaler handling errors negatively impact asthma control and represent one of the most common challenges in asthma management. Overcoming inhaler handling errors can be achieved by increased awareness of errors, more explicit and consistent training in inhaler use, and development of 'intuitive' devices. Clinical studies have shown that dry powder inhalers (DPIs) have better dose consistency and delivery to the lungs, but this is also dependent on device and inhalation technique. In addition, recent clinical studies have demonstrated that Spiromax® is a more intuitive device than Turbuhaler®. In studies analysing patient device mastery, intuitive devices are preferred by patients because they are easy/simple to use and have effective dose delivery.

Are Inhalers Failing Our Patients?

Professor Gary Wong

The inhaled route for the administration of steroids for asthmatics has been used for more than 60 years, and the majority of asthma treatments are directed against Th2-type inflammation. A variety of guidelines to treat asthma are established worldwide. The Global Initiative for Asthma (GINA) guidelines[1] provide stepwise management using pharmacotherapy. Despite the availability of a wide variety of medications, a significant portion of asthmatic patients have poorly controlled asthma. This was shown in the Asthma Insights and Reality in Asia-Pacific (AIRIAP 2) study, in which over 50% of children in this region were found to have poorly controlled asthma.[2] To address this issue, there is a need to understand whether patients with uncontrolled asthma need extra medication or whether they are using their inhalers incorrectly.

Patients who are 75–100% adherent to taking their medication are half as likely to have an asthma exacerbation.[3] In addition, patients who do not use their inhalers correctly are more likely to have poor adherence to their medication.[4] Therefore, the correct use of inhalers is heavily reliant on patient behaviour. Patient behaviour influences correct use of inhalers in three ways: 1) competence: the patient can use the device in the correct manner; 2) contrivance: the patient has the knowledge to use the device correctly, but does not use the inhaler as instructed once they have left the clinic; and 3) compliance: the patient takes the medication as recommended. It is therefore important to have simple devices that are easy both for the physician to demonstrate to patients and for patients to use.[5,6]

In summary, inhaled corticosteroids, delivered via inhaler devices to minimise possible systemic adverse effects, are the standard of treatment for asthma. Ineffective inhaler use resulting in poor asthma control is a major problem for patients with asthma. Factors influencing inhaler technique include the availability of training with the prescribed device(s), patient preference and satisfaction, and their physical ability to use the device.

Improving Patient Outcomes and Adherence in Asthma: All Devices Are Not Equal

Professor J. Christian Virchow

Due to the undesired long-term adverse effects of systemic administration of corticosteroids, inhalation therapy is the most effective targeted treatment for airway diseases. Inhalation therapy provides high local concentrations of medication with low systemic effects. Therefore, the inhaler device itself is crucial for drug delivery. Poor asthma control is often a result of underestimation of disease severity, ineffective treatment guidelines,[7] wrong/incomplete diagnosis,[8] or delay in diagnosis. In addition, further reasons for poor asthma control include poor treatment compliance, wrong inhaler choice, insufficient inhaler instructions, and poor inhaler technique.[7] While there are marginal differences in the efficacy of available medications, the choice of inhaler device and inhaler technique has a huge impact on asthma control and thus the healthcare system costs for asthma patients. Inhaler misuse is associated with decreased asthma stability and therefore good adherence to treatment is not helpful if a patient has poor technique.[9] In a study of children with severe asthma, improving inhalation technique from 65–95% resulted in improved asthma control and a reduction in required daily corticosteroid dose.[10]

Assessing adherence is difficult as several parameters need to be taken into consideration, including patient reports, dose counters, and weighing, all of which carry a degree of imprecision in data reporting. All of these are subject to manipulation: selection bias of the patient population and patients' temporary adherence for the sake of the trial. A recent study analysed patient adherence utilising electronic monitors versus a self-reported questionnaire. The self-reported questionnaire overestimated inhaler use by a mean of 2.2–8.4 inhalations over a 1-week period (limits of agreement: ±15.8–25.6 inhalations).[11] This was a result of over-users under-reporting, and under-users over-reporting, their medication use. These discrepancies may be due to patients forgetting, or trying to please the caregiver by confirming that they followed instructions.

New strategies are being studied to improve adherence. One such study analysed inhaler reminders versus behaviour intervention in which doctors have a personalised discussion with

patients about the necessity of treatment.[12] Electronic reminders were demonstrated to improve adherence at both time points used (6 months and >6 months). In addition, adherence is not the same thing as compliance: patients often do not take their medication once they feel better, which is acceptable provided that the patient achieves his/her personal goals without increasing healthcare resource utilisation. A recent study showed that mild-to-moderate asthmatics can effectively manage their medication themselves, while moderate-to-severe asthmatics have better symptom control while taking their medication regularly.[13]

It is important to utilise the 'most forgiving device' with which there are no crucial errors made during drug delivery. A minimally complicated process of 'exhale–open–inhale–close' is the least complicated, most forgiving technique. In order to improve adherence, the patient's choice of device and technique should also be taken into account. A safety and efficacy study compared Spiromax with Turbuhaler over 12 weeks in which the same medication was used in the two devices (the ASSET study).[14] In this study, patient satisfaction was greater with Spiromax and more patients were willing to continue treatment with Spiromax past the 12-week study period.

In summary, adherence to therapy is an important consideration in asthma management. Allowing patients to choose which inhaler technique they prefer is likely to influence treatment success and should be considered an integral part of asthma management.

Can an Intuitive Device Reduce Critical Errors?

Professor Richard Dekhuijzen

Slow inhalation and (almost) simultaneous activation of the canister is the correct way to use pressurised metered-dose inhalers (MDIs). However, almost 25% of patients with asthma or chronic obstructive pulmonary disease (COPD) use their inhaler incorrectly, which impacts drug delivery, lung deposition, and disease control. For MDIs, 92% of patients fail to use slow, deep inhalation,[15] 54% fail to coordinate inhalation with actuation, 24% have premature cessation of inhalation, and 12% inhale through the nose.[16] In addition, patients also fail to shake their inhaler before actuation or fail to hold the inhaler upright.[15-17] For DPIs, the correct usage is the generation of a forceful and deep inhalation. Failure to achieve this at the start of inhalation results in drug particles being deposited in the mouth and oropharynx.[18] DPI devices are also dependent on correct orientation of the device and inspiratory effort to achieve adequate inhalation volume.[18,19] Errors may lead to insufficient drug delivery, which adversely influences drug efficacy and may contribute to inadequate control of asthma and COPD. Overall, the design of an intuitive inhaler that is simple to understand and easy to open should reduce the number of critical errors.

GINA guidelines[1] recommend that healthcare professionals (HCPs) train and assess patients on device mastery at every visit, and recommend HCP training in device use. A second randomised, cross-over, observational trial (HCP-ELIOT) was performed to compare maintenance of device mastery with Spiromax versus Turbuhaler in HCPs naïve to both devices. HCPs were exposed to the same training levels as patients in the ELIOT study. Overall, significantly more participants achieved device mastery with Spiromax prior to training or after reading the manufacturer's instructions compared with Turbuhaler. In addition, participants using Spiromax required fewer device training steps in order to achieve device mastery compared with those using Turbuhaler. In conclusion, significantly more participants using Spiromax achieved device mastery in fewer steps with fewer errors, although it must be noted that this is an interim analysis of the data.

A Real-Life Inhaler that the Patient Can and Will Use: What Are We Still Missing?

Professor Henry Chrystyn

The key criteria to be considered for any 'real-life' inhaler include that it be effective and well tolerated, easy and simple to use, preferred by patients, cost-effective, and that it provides a consistent dose to the patient.[20,21] Most importantly, it should be a device that patients can and will use.[21] The problems with current inhalers include dose emission variation and common errors in dose preparation and inhalation manoeuvres (Table 1).

Table 1: Problems with inhaler use.

Aspect of inhaler use	Metered-dose inhaler devices	Dry powder inhaler devices
Metered-dose/dose emission	Consistent	Ranges from erratic to consistent
Dose preparation	Errors common	Errors dependent on device
Inhalation manoeuvre	Errors common	Errors common

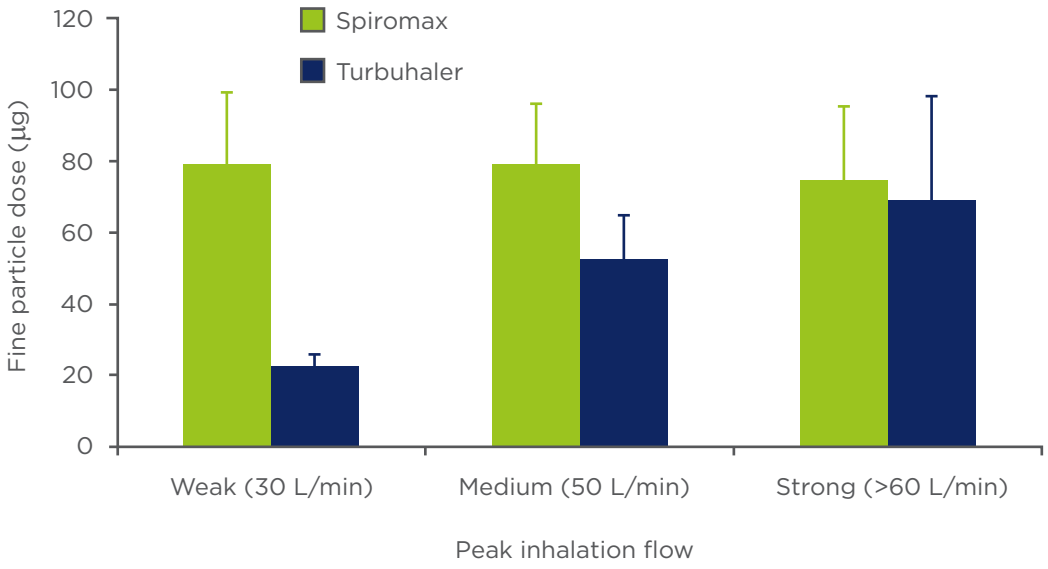

Figure 1: Mean (standard deviation) fine particle dose emission from 320/9 µg budesonide/formoterol dry powder inhaler using different inhalation profiles (weak, medium, and strong peak inhalation flow).

Currently, MDIs are the most commonly prescribed treatment worldwide, with a wide range of products that are cost-effective and have consistent dose emission, but inhalation errors are still common.[17,22-27] Electronic monitoring of training techniques in the use of MDIs revealed that, even after the third attempt, over 54% of patients fail the inspiratory flow criterion.[28] A recent study has shown that there is a significant improvement in asthma control when using an MDI with slow inhalation.[15] In addition, the increased deposition of the drug into the lung observed with slow inhalation can offset any lack of coordination of actuation.[29] However, most patients inhale too fast and the recommended instruction to use an inhalation that is "steady and deep" is subjective and interpreted differently by users and trainers. A recent study has shown that defining this instruction as an inhalation that takes an adult approximately 5 seconds to complete will ensure the required slow inhalation flow when using an MDI. When adult patients with asthma were given this instruction verbally, the result was a dramatic reduction in their peak inhalation flow when using their MDI. This slow flow was maintained when they demonstrated the use of their inhaler 4 weeks later without any further training.[30]

Studies of dose emission for DPIs have shown that dose delivery varies according to the DPI.[31,32] In contrast, analysis of DuoResp® (BF) Spiromax dose emission throughout the life of the inhaler (beginning, middle, and end of life) at three doses (low, medium, and high strength) revealed very consistent emitted doses.[33]

Patient technique for using DPIs can be divided into two categories: the inhalation manoeuvres and dose preparation.[24,26] The incidence of errors with respect to the inhalation manoeuvre is independent of the DPI used. However, DPIs differ in terms of dose preparation.[24,26] Inhalation errors include not exhaling, not inhaling fast, inhaling too short, and not holding the breath. As dose preparation for each device is different, they should not be classified as generic products. The Turbuhaler is associated with two critical errors: 15% of patients performed only a one-side twist, and 18% did not hold the device in the correct orientation when

preparing a dose, which results in the dose not being loaded.[26] Spiromax, on the other hand, can be used in any orientation to achieve dose loading and emission.[33] Dose preparation errors with this device should therefore be lower and its use should be more intuitive.

A recent study has analysed the variability in how patients use inhalation devices across age groups and disease states. Children and patients with COPD were observed to inhale more slowly, and faster inhalation was seen with Spiromax versus Turbuhaler.[34] *In vitro* analysis of fine particle dosing demonstrated that Turbuhaler has a steep flow-dependent dose emission,[31,32] but this study was performed using a vacuum pump, which does not produce physiologically relevant inhalation values. Using inhalation profiles from Spiromax and Turbuhaler studies[34] instead of a vacuum pump revealed that the Turbuhaler is subject to a traditional flow-dependent dose emission while Spiromax delivers a consistent dose regardless of the inhalation profile (Figure 1).[35]

In summary, MDI inhalation technique can be improved by training patients to perform a slow and deep inhalation, in which they actuate a dose and inhale while counting to 4–5 seconds (2–3 seconds with a child). DPIs are subject to dose preparation errors, which can be solved by a device that is intuitive/simple to use and minimally affected by device orientation. Inhalation manoeuvre errors can be minimised by choosing devices that have minimal flow-dependent dose emission.

Q&A session

How do we address the issue that the more devices there are for asthma and COPD, the more difficulties there are for paramedical personnel, primary care physicians, and patients?

Prof Virchow replied that it is not a negative thing to have more options to choose from in order to provide the patient with a device that is reliable and user-friendly to them. It is important to give patients devices requiring the same inhalation technique so as to not create confusion between devices. Research is getting closer to the development of an optimal inhaler and physicians need to try to match inhalers to what patients want. An important topic for the future is to make all drugs available in a single inhaler type instead of having to give different inhalers to one patient. Prof Chrystyn added that there is only one generic MDI. Most DPIs are branded products with different dose preparation steps, and new inhalers should include a range of therapies, including short-acting beta-agonists.

Some MDIs and DPIs resemble one another, so should extra care be taken to instruct patients in preparing a device and using it correctly?

Both Prof Chrystyn and Prof Virchow agreed that it is very important to train patients about the specific techniques and specificities for any inhaler, especially if devices look similar.

Is there any way to address the issue of patient compliance? What do physicians do when patients know how to use a device but choose not to?

Prof Wong replied that it is important to have a good rapport with the patient. You can rely on relatives a little to give an honest answer about inhaler use, but it is also important not to judge when asking about medication usage. He also recommended that physicians listen carefully to the feedback from their patients. It can be helpful to try different devices in order to find something that they are willing to use.

Why is the dose emission lower in the beginning of the inhaler's life and does this have any clinical importance?

Prof Chrystyn replied that it was only slightly lower and was within regulatory ranges. He stated that the reason for this minimal difference is not known, but speculated that it may be because the inhaler contains more in the reservoir at that point.

Is there any future for MDIs?

Prof Chrystyn emphasised that there is a future for MDIs. The main issue is to better train people to use the inhalers. Being able to define a slow and deep inhalation would make a huge difference. Prof Dekhuijzen added that the majority of asthma drugs prescribed worldwide are provided via MDIs.

What should be the current working diagnosis? Should physicians first select which molecule to prescribe or should they pick a device first?

Prof Dekhuijzen suggested that physicians should first think about the device before selecting the type of drug, because there are many drug classes available and minimal differences in efficacy among drugs.

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