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REVIEW

Prescription of inhalers in asthma and COPD: Towards a rational, rapid and effective approach

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Summary
Inhaled medication is the cornerstone of the pharmacological treatment of patients with asthma and COPD. The major two classes of inhaled medication include corticosteroids (ICS) and bronchodilators. There is a wide diversity in molecules in both classes. Moreover, there is a wide variation in delivery systems.

The correct use of inhalers is not granted and patients often incur in many mistakes when using pMDIs and DPIs, despite repeated instructions. A better matching between patient and device could be accomplished if the physician is aware of: (1) the patient characteristics (disease, severity, fluctuation in airflow obstruction, etc); (2) what class of medication is

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indicated; (3) where in the lung the medication should be delivered; and, (4) how this can be best achieved by a given device in this specific patient.

We focus on the prescription of pMDIs and DPIs at the GP office or at the outpatient clinic of the hospital, and we propose an evidence based approach enabling the caregiver to make a rational choice in only a few minutes by just considering the following four simple questions: Who?, What? Where? and How? (the so-called 3W—H approach).

Contents

Introduction

Inhaled medication is the cornerstone of the pharmacological treatment of patients with asthma and COPD. The major two classes of inhaled medication include corticosteroids (ICS) and bronchodilators. There is a wide diversity in molecules in both classes. Moreover, there is a wide variation in delivery systems. The most frequently used are pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) [13].

When prescribing a specific inhaler device, clinicians should consider a number of factors, including the ability to generate an adequate inspiratory flow, the capacity to handle the device appropriately and, importantly, its co-ordination with the inspiratory effort.

However, the correct use of inhalers is not granted and patients often incur in many mistakes when using them [6,8,10,15]. Mistakes are made both with pMDIs [14] and DPIs [12], despite repeated instructions [20]. These instructions should be uniform among all caregivers but this is often not the case. In addition, reduced adherence and compliance are associated with misuse of inhaler device on the one hand and have been linked to poor asthma control [5] and COPD outcomes on the other [7]. This may increase morbidity and perhaps even mortality. Clearly, this impacts on the financial costs of treating these patients [9]. These and other factors are summarized in Table 1 and may negatively influence the optimal use of inhalers (Table 2).

A better matching between patient and device could be accomplished if the physician is aware of: (1) the patient characteristics (disease, severity, fluctuation in airflow obstruction, etc); (2) what class of medication is indicated; (3) where in the lung the medication should be delivered; and, (4) how this can be best achieved by a given device in this specific patient.

The aim of this paper is to assist the caregiver in prescribing inhaled in prescribing the most appropiate inhaler for adult patients by using a evidence-based rational and effective approach. We focus on the prescription of pMDIs and DPIs at the GP office or at the outpatient clinic of the hospital, and we propose an evidence based approach enabling the caregiver to make a rational choice in only a few minutes by just considering the following four simple questions: Who?, What? Where? and How? (the so-called 3W—H approach).

Who? consider asthma and COPD disease characteristics

Firstly, it is important to determine if a patient has asthma or COPD (or an overlap syndrome). In some cases, the diagnosis might have been already established but suggestive features of COPD and asthma are listed in Table 1 [17]. Both in asthma and COPD there is a wide spectrum of severity, with wide variations in levels of airflow limitation, level of hyperinflation at rest and during exercise, and the work of breathing in stable and unstable disease. It is important to consider these aspects because they may eventually influence the choice of a specific device. Ideally, the device should be suitable for a specific patient in stable and unstable clinical conditions. An important determinant is his/her ability to generate adequate inspiratory flow, especially in the case of a DPI. In patients with severe hyperinflation (as it occurs in some patients with COPD and during asthma attacks) inspiratory flow rate may be reduced. In addition, inspiratory muscles may be at mechanical disadvantage in the presence of severe hyperinflation. This may contribute to the sense of dyspnoea during inhalation via a DPI and may thus reduce efficacy. Other issues to consider include the presence of comorbidities (e.g. arthritis) which may affect inhaler handling.

What? consider the type of drug to use

Inhaled corticosteroids (ICS) are the cornerstone of anti-inflammatory treatment in patients with asthma. Several

Table 1 Important factors to consider when selecting an inhaler device for a specific patient.

Patient-related factors	Including (i) the ability to inhale consciously, handle the device and coordinate the use of the device and the inspiratory effort, (ii) patient's preference and (iii) adherence and compliance. Other factors may include age and comorbidities.
Disease-related factors	Since (i) severe and/or acute airflow obstruction may compromise the ability to generate an adequate inspiratory flow and (ii) therapeutic strategy and indications not the same for asthma and COPD.
Device-related factors	As the optimal inhalation profile differs between pMDIs (slow inspiration is preferable) and DPIs (high-flow inhalation in required, with fast acceleration especially for reservoir devices).
Caregivers-related factors	Accounting for the availability and knowledge of professionals involved in information and education (general practitioners, specialists, nurses, physiotherapists, pharmacists).

ICS are available, with some differences with regard to local potency, oropharyngeal side effects, and particle size (see below). In patients with more than mild asthma, the combination of an ICS and a LABA in one inhaler is often prescribed.

In COPD, the primary pharmacologic intervention consists of long-acting inhaled bronchodilators. The response of patients to inhaled anticholinergics, beta agonists and the combination of these two may vary. Lung function response is a poor predictor of clinical response, which has to be prioritized. The initial and subsequent choices may also be influenced by the existing comorbidity and potential side effects of inhaled bronchodilators. For example, β2 agonists should be avoided in patients with tremor. Anticholinergics should be avoided in case of glaucoma and a history of urinary retention. A debate is still going on what to choose for patients with high risk of rythmic and/or ischaemic cardio-vascular side-effects, since both anticholinergics and β2 agonists may lead to such effects.

Where? targeting the medication

Bronchial asthma is characterized by an eosinophilic inflammatory process in the airways, which is present throughout all airways, both the large airways and the small peripheral airways with a diameter of 2 mm and less. These small airways comprise most of the airway surface in the lungs. In addition, this inflammatory process extends even to the alveolar compartment. This so-called peripheral inflammation may be related to the clinical manifestation of the severity of asthma. The periphery of the lung contains a very high concentration of steroid receptors [1]. Targeting the small airways with ICS with a small particle size and a high peripheral deposition may result in better control of the disease in a subset of patients. Indeed, several clinical-mechanistic studies have shown that, in contrast to the 'conventional' ICS with 'large' particles, these ultrafine ICS may induce functional and immunologic alterations in the peripheral lung compartment [18].

The pathology in COPD is characterized by inflammation, mucus hypersecretion, oedema, bronchospasm and in case of emphysema, loss of alveolar retraction forces. All these changes reduce the patency of the small airways. Maximal bronchodilatation (e.g. bronchiolodilatation) thus reduce air trapping at rest and during exercise [11]. β-2 receptors are present everywhere in the lung, with the highest concentration in the periphery of the lung [2]. Cholinergic receptors are also present everywhere in the airway walls,

Table 2 Suggestive features for differential diagnosis of COPD and asthma from [17].

Table 1. Suggestive features for differential diagnosis of COPD and asthma [1,12].

	COPD	Asthma
Onset	Mid-life (rare before age 35)	Early life, usually childhood
Symptoms	Typically dyspnoea, cough, mucus production Slowly progressive Dyspnoea during exercise	Typically dyspnoea, cough, chest tightness, wheeze (often occurring at night or early morning) Vary from day to day (can improve with removal of triggers) Dyspnoea after exercise
Smoking history	Long history of tobacco smoking likely (current or ex-smoker)	Possible
Co-morbidities	Chronic diseases common, e.g. heart disease, osteoporosis, diabetes, depression	Allergy, rhinitis and/or eczema often present
Family history	History of obstructive airway disease increases risk	Family history of asthma or allergy increases risk 2—6-fold
Airflow obstruction	Not completely reversible	In most instances completely reversible

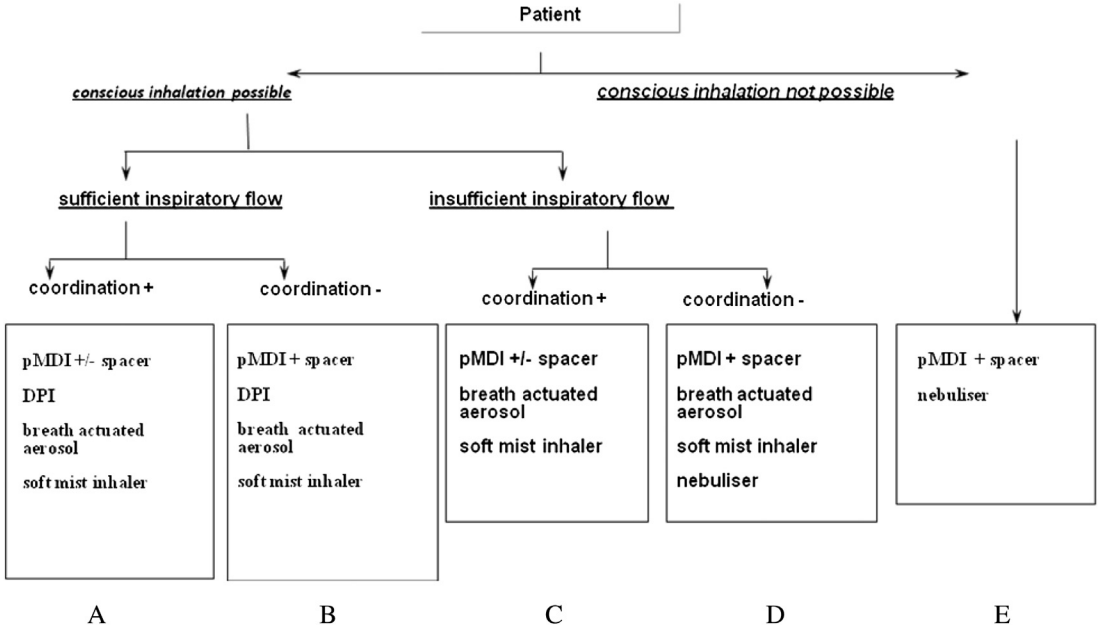

Figure 1 Choosing an inhalator: decision tree in adults with COPD and asthma from [4].

but with a somewhat higher concentration in the more proximal airways [3].

How? matching patient, molecule, dose and device

We propose that the choice for a particular inhaler device in a given patient should follow the algorithm shown in Fig. 1. The first step addresses the issue of whether the patient can inhale medication consciously. Elderly patients with cognitive limitations are limited in these abilities. The second step addresses the issue of whether the patient can generate a minimal inspiratory flow. Patients with COPD and severe hyperinflation and asthma patients during exacerbations may have reduced ability to generate an adequate inspiratory flow rate through DPIs, especially those with a high internal resistance [19]. Finally, the third step concerns adequate hand-lung coordination. According to this algorithm, Fig. 1 proposes different options (Blocks A to E) to be considered in different patient types.

Block A refers to patients with adequate inspiratory flow rate and good coordination. Any available DPI and pMDI can be prescribed. In case of oropharyngeal complaints a pMDI with a low oropharyngeal deposition or a traditional pMDI combined with a spacer should be considered.

Block B relates to patients with sufficient inspiratory flow but poor hand-lung coordination. A traditional pMDI is not sufficient in this case. Options now include a new pMDI with a low oropharyngeal deposition, a breath-actuated pMDI, and a pMDI with spacer.

Block C includes patients with insufficient inspiratory flow but adequate coordination. Examples are severe COPD patients and patients with severe asthma and recurrent exacerbations. Options now include a usual pMDI, a breath-actuated pMDI and a pMDI with a spacer.

Block D refers to patients with insufficient inspiratory flow and insufficient coordination. Options now include a breath-actuated pMDI and a pMDI with a spacer.

Finally, Block E relates to patients who are not able to inhale medication consciously. A pMDI with spacer or a nebulizer should be considered in this situation.

In addition it is important to try to avoid mixing devices (e.g. pMDI and DPI) in the same patient. It is difficult to remember technique for both and there is evidence that mixed devices are associated with worse disease control in asthma [16].

Conclusion

An optimal match between patient and device may be achieved by applying a simple four-model (3 W—H) question (Who-What-Where-How) approach. We recognize that this is an empirical proposal that needs prospective experimental validation but we hope that, in the meantime, physicians around the globe may find it helpful to make the best inhaler device choice for patients with chronic airway disease.

Conflicts of interest

Richard Dekhuijzen has received reimbursements for attending symposia, fees for speaking, organising educational events, funds for research or fees for consulting from AstraZeneca, Boehringer-Ingelheim, Chiesi, Merck Sharp & Dohme, Mundipharma, Novartis, Takeda, Almirall and Teva.W. Vincken has received reimbursements for attending symposia, fees for speaking or fees for consulting from AstraZeneca, Boehringer-Ingelheim/Pfizer, Chiesi, GlaxoSmithKline, Meda Pharma, Mundipharma and Novartis. He is member of the Aerosol Drug Management Improvement Team (ADMIT).J.C. Virchow has received

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D. Price has received reimbursements for attending symposia, fees for speaking, organising educational events, funds for research or fees for consulting from Almirall, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycomed, Pfizer, Sandoz and Teva.

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