Budesonide Modulite®: Improving the changeover to CFC-free treatments

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Introduction

The transition from CFC to HFA metered dose inhalers has improved asthma therapy

Inhaled corticosteroids have been recommended by national and international guidelines as the mainstay for anti-inflammatory treatment in patients with bronchial asthma. Inhaled corticosteroids are delivered by a variety of devices such as pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulizers. The choice of the devices is dependent on a number of clinical factors such as severity of the disease, ability of the patient to proper usage of the device and the preference of the patient and the doctor. The latter is not always based on strong arguments.

Inhalation therapy for treatment of bronchial asthma is performed since more than 200 years using "asthma cigarettes". The first Jet-Nebulizers were brought up in the 1930s, and in 1956, the first CFC-containing pMDI was marketed (Riker Medihalets). These devices were mainly used to deliver inhaled beta-agonists and anticholinergics to the patient, with the benefit of rapid onset of action as compared to the traditional oral route. It took nearly 20 years to develop an inhaled corticosteroid with limited side effects due to a significant first pass metabolism. Dry powder inhalers were developed later. The majority of asthmatic patients is using pMDIs worldwide. The popularity of these devices is based on their design as they are easy to use, small and portable. pMDIs designed by different companies look much more alike than DPIs.

The effect of a certain drug delivered by the respiratory route is dependent on a variety of different factors which amongst others are the ability of the patient to inhale correctly and to produce a sufficient inspiratory flow. Drug deposition and the local and systemic metabolism of the compound are important factors determining the effect and the side-effects. Recently, the technology to design and produce devices for respiratory delivery has improved markedly. However in contrast to the progress in inhaler technology, adherence and compliance to the recommended therapy with inhaled corticosteroids remain a serious problem which has to be minimized in order to ensure the clinical benefit of inhaled corticosteroids in patients with bronchial asthma.

Chlorofluorocarbons (CFCs) have been used in many products such as refrigeration, plastics, non-medical aerosol, etc. pMDIs traditionally have been formulated using CFC propellants 11 and 12. The emission of CFCs into the atmosphere is harmful to the ozone layer. This resulted in an Environmental Program under the auspices of the United Nations, and over 40 nations agreed to the Montreal protocol in 1987 for the reduction and later for the cessation of the use of CFCs. The production of CFCs was stopped in 1996 except for "essential uses". Essential uses included the manufacturing of pMDIs containing drugs for patients with airway diseases (asthma and COPD) and on therapy with pMDIs. The European Commission (Strategy for the Phase-Out of CFCs in Metered Dose Inhalers) decided later the criteria according to which CFC containing inhalers should be withdrawn.

After years of research in this area, hydrofluoroalkane (HFA) 134a (norflurane) was selected as a

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potential substitute for CFC in pMDIs. Many pharmaceutical companies started programmes to develop norflurane-based pMDIs containing β-agonists and corticosteroids. The principal objective of these research programs was a smooth transition from CFC to non CFC pMDIs.

However, CFCs and HFAs share a number of basic technical characteristics but differ in such physical properties as density, vapor pressure, molecular polarity and evaporation kinetics. Therefore, the initial idea that CFC formulations can be translated into HFA ones without any major changes was one of the most cost-intensive mistakes of the pharmaceutical development. These differences have necessitated the development of new formulations, valves and manufacturing processes for HFA-134a inhalers. However this technical research was a potential milestone in aerosol therapy, as new questions were raised, and new formulations like the extrafine aerosols were developed.

Different topics have to be addressed when new inhalers or propellants are developed. The first and most important is that the active drug has to be formulated with the propellant. The traditional CFC devices contain the active drug in suspension, but the active is, as in the case of beclometasone and budesonide, partially soluble in norflurane; in some instances drugs were reformulated as suspension formulations, while in other cases solutions have been obtained with the use of a co-solvent. For the replacement of CFC-containing propellant two different strategies are available: one is heading for an “extrafine” aerosol, resulting in increased efficacy, but potentially reduced therapeutic ratio. The other way is to leave the dose and particle size as they are in the CFC-devices, and the patients can continue with the same dose they are used to.

The Chiesi Group has developed technical solutions to allow phaseout of CFCs and replacement with HFAs. The development program was aimed at producing tailored particle aerosols which allow an easy transition to CFC-free products because the dose remains the same, but also optimize the intrapulmonary deposition of the inhaled drugs. This last point reiterates the importance of the small airways in bronchial asthma. To investigate small airways is a real challenge as conventional lung functions test are insufficient to differentiate between the functional contribution of small versus large airway. The introduction of methods to investigate airway inflammation by invasive (bronchoscopy, bronchoalveolar lavage) and non-invasive (induced sputum, exhaled air, breath condensate) techniques allowed new insights in the distribution of airway inflammation along the airways. Lung slices taken from human lungs allowed to investigate small airways and to study the response to pharmacologic interventions. Recent advantages in high-resolution computed tomography imaging have allowed to study the structure function relationship in the small airways and in vivo assessment of drug deposition. Thus the transition of CFC-based pMDIs to HFA containing devices resulted not only in progress of inhaler technology but prompted intensive research in the field of small and peripheral airways which has been neglected over the last few decades.

In this supplement of Respiratory Medicine a new formulation of the well-known inhaled corticosteroid budesonide in HFA134a is presented. This is the first available HFA-budesonide on the market and it has been developed by Chiesi Group using the proprietary technology Modulite®. Key advantages of the Modulite® technology are stable and uniform dose delivery of HFA-based formulations and flexibility in tailoring the particle size distribution of the cloud generated on actuation of the pMDI. The new HFA-budesonide is a solution formulation and has been designed to be equivalent in terms of efficacy, safety and dose delivered to currently marketed CFC-containing inhalers, so as to allow a “seamless” transition to the CFC-free pMDI.

In the first article, Ganderton et al.9 carefully describe problems and solutions of the formulation and evaluate the new CFC-free budesonide pMDI. This study demonstrates the translation of improvements in designing pMDIs into clinical benefits like reduction in oropharyngeal deposition.

Comparative clinical studies have to be made to reassure that new formulations of established treatments have the same safety and tolerability, as well as equivalent efficacy of available drugs. Therefore, in this issue of Respiratory Medicine two studies are shown that report on the asthma control, efficacy and safety profile of the new HFA-budesonide formulation.

The aim of these studies was to show equivalence of the HFA-budesonide as compared to the CFC-containing pMDIs to assure a dose per dose transition.

In the first study, Grzelewksa-Rzymowska et al.10 showed no differences in efficacy and safety between HFA and CFC-containing budesonide pMDI.

The second study of Vastagh et al.11 was capable to show similar efficacy to the clinical parameters like PEFR, rescue salbutamol use and symptom score in mild to moderate asthmatic patients using either CFC-budesonide or HFA-budesonide b.i.d., or the identical daily dose of HFA-budesonide as a single morning dose. A more or less identical efficacy profile and safety profile was found. This is of special
interest for the ongoing debate about the use of once daily inhaled corticosteroids that are currently under clinical assessment. It would be of special interest if the HFA-budesonide is comparable to the new inhaled steroids like ciclesonide or mometasone, that claim for a once-daily application.

All studies presented here and those related to the replacement of CFC by HFA containing pMDIs are part of a challenging history leading to improvements in asthma therapy.

References