South African Family Practice 2018; 60(3):5-6

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

PRODUCT FOCUS

Focus on Innuvair® Inhaler for Asthma

J Van Schoor

Amayeza Information Centre
**Corresponding author, email: jacky@amayeza-info.co.za*

Republished with permission: *S Afr Pharm J* 2018; 85(3):39-40

Introduction

The long-term goals of asthma management are to achieve good symptom control, to maintain normal activity levels and to minimise future risk of exacerbations, fixed airflow limitation and side-effects of treatment.[1] The 2017 Global Initiative for Asthma (GINA) guidelines recommend that treatment with regular daily low-dose inhaled corticosteroids (ICS) is highly effective in reducing asthma symptoms and in reducing the risk of asthma-related exacerbations.[1] For patients with persistent symptoms and/or exacerbations despite low-dose ICS, the preferred step-up treatment (Step 3) is combination low-dose ICS/long-acting beta$_2$-agonist (LABA) therapy.[1]

A new ICS/LABA combination

Innuvair® inhaler contains the ICS/LABA combination of beclomethasone dipropionate and formoterol.[2] It is indicated in South Africa for the regular treatment of asthma in adults where use of a combination product is appropriate[2]:

- Patients not adequately controlled with inhaled corticosteroids and an 'as-needed' inhaled short-acting beta$_2$-agonist
- Patients already adequately controlled on both an inhaled corticosteroid and a long-acting beta$_2$-agonist

A new technology

The phasing out of chlorofluorocarbons (CFCs) led to the development of pressurised metered-dose inhalers (pMDIs) that use hydrofluoroalkane (HFA) propellants.[3] More recently, using Modulite® technology, new pMDIs have been developed which use compounds reformulated into solutions (as opposed to currently available HFA suspensions).[3] While HFA suspensions retain the same particle size, deposition and efficacy profiles as their CFC counterparts, HFA solutions can be manipulated to vary particle size distribution permitting precise control of delivered dose and optimised drug delivery to allow the drugs to penetrate the deeper regions of the lung more effectively.[4]

Innuvair® inhaler, developed with Modulite® technology, contains 'extra-fine' drug particles with a particle size less than 2 µm, which is suitable for homogeneous distribution of the medication throughout the bronchial tree.[5] The rationale for developing an extra-fine formulation lies in the fact that asthma is characterised by airway inflammation in the entire lung, including the large as well as the small airways.[6]

Reaching the small airways

Lung deposition is a critical factor for the optimal treatment of asthma and particle size is a major determinant of the proportion of drug that reaches the lung.[4,7] Inflammation of the small airways (internal diameter less than 2 mm) is an important feature of asthma and treatment of inflammation in both the large and the small airways may be key for effective asthma control.[7]

Most conventional inhaler devices achieve relatively poor levels of total lung deposition (TLD).[8] At best, 10–20% of the inhaled drug deposits in the lungs, leading to four-fifths of the dose being wasted.[8] Inhaler devices that can emit smaller drug particles at slower velocities achieve better total lung deposition (30–50%) and importantly, allow effective penetration of the drug into the smaller airways.[8] Deposition studies in asthmatic patients with Innuvair® inhaler showed approximately one-third peripheral (small airway) deposition and two-thirds central (large airway) lung deposition as a proportion of total lung dose.[8]

Taken together, lung deposition data in asthmatic patients show that extra-fine aerosols not only achieve better lung deposition, but also effective penetration into the peripheral lung, thereby reaching not only the large but also the small airways.[8]

ICS dose reduction

The beclomethasone dipropionate/formoterol 100 µg/6 µg pMDI is an extra-fine solution formulation in which the beclomethasone dipropionate (BDP) dose is 2.5-fold lower than conventional beclomethasone dipropionate CFC formulations (100 µg of BDP per actuation instead of 250 µg of non-extra-fine BDP).[6] The dose reduction is possible due to improved lung deposition of a smaller particle.[9]

The reduction in BDP nominal dose, together with the extra-fine particle size, allows a similar dose of the drug to reach the lower airways and less drug to be deposited in the upper airways, potentially improving the efficacy/safety ratio of the ICS.[6]

Therapeutic efficacy

Although beclomethasone and formoterol are well-known molecules of proven efficacy and safety, the clinical development of the extra-fine beclomethasone/formoterol combination involved a series of clinical trials conducted in patients with asthma.[7] Clinical trials were designed to explore whether use of extra-fine formulations improved lung function, asthma control and health-related quality-of-life compared with inhaled drugs delivered as non-extra-fine formulations.[10]

The efficacy of the beclomethasone dipropionate/formoterol (BDP/F) combination was evaluated in a three-month randomised controlled trial in patients with moderate to severe asthma who were still symptomatic despite receiving low-dose ICS (up to 500 µg of BDP or equivalent).[6]

- Extra-fine BDP/F given as one inhalation twice daily proved to be more effective at improving lung function than a double equipotent dose of BDP non-extra-fine.[6]

A second investigation was carried out in patients with more severe asthma, documented by recurrent symptoms and impaired lung function despite treatment with up to 1 000 µg/day BDP or equivalent.[6]

- Extra-fine BDP/F given as two inhalations twice daily showed improvement in peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1), comparable with that of an equipotent non-extra-fine regimen of BDP and formoterol administered via separate inhalers.[6]
- Furthermore, the extra-fine BDP/F fixed combination was superior to BDP plus formoterol in separate inhalers in terms of asthma control.[6,7] This study represents the first randomised controlled trial to show a difference in asthma control between an ICS and a LABA administered as a fixed combination compared with separate inhalers.[6,7]

Two head-to-head clinical trials assessed the efficacy and tolerability of BDP/F versus budesonide/formoterol and versus fluticasone propionate/salmeterol in patients with moderate to severe asthma.[6,11,12]

- In the first trial, patients given BDP/F as two inhalations twice daily showed improvement in lung function, measured by morning pre-dose PEF, which was comparable with that of an equipotent regimen of budesonide/formoterol (200/6 µg) administered as two inhalations twice daily.[6,11] Both therapies were equally effective at improving asthma symptoms and increasing the percentage of days without the use of rescue medication.[6,11]
- In the second trial, BDP/F was compared with fluticasone propionate/salmeterol pMDI, both administered as two puffs twice daily.[6,12] BDP/F demonstrated improvement in PEF and FEV_1 comparable to that of fluticasone propionate/salmeterol.[6,12] However, the extra-fine BDP/F combination demonstrated a greater and more specific effect on variables directly related to small airways function, as shown by the significant difference in forced vital capacity (FVC).[6,10,12]

The above studies are controlled clinical trials involving highly selected asthma patients fulfilling strict inclusion and exclusion criteria, which may not reflect patients seen in 'real-life' daily clinical practice.[8]

- Real-life studies with Innuvair® inhaler have shown significantly higher levels of asthma control, better quality of life and the use of lower daily ICS doses when compared with large particle ICS/LABA pMDIs.[8]

Safety and tolerability

BDP and formoterol are not new chemical entities and are therefore not likely to expose patients to the risk of unexpected or unknown side-effects.[6] The lower dose of the ICS, as a result of the improved drug delivery of the extra-fine formulation, results in an improved safety margin due to less drug being available for systemic absorption.[10] In addition, reduction in the amount of ICS deposited in the oropharynx limits local side-effects of the ICS, such as hoarseness, dysphonia and candidiasis.[10]

Key issues

The new fixed combination of beclomethasone/formoterol has the following properties:

- Extra-fine hydrofluoroalkane-propelled solution, characterised by a small particle size and high particle deposition throughout the bronchial tree (Modulite® technology).[13]
- High efficacy coupled with low systemic bioavailability.[13]
- Comparable efficacy on lung function and a greater efficacy in terms of asthma symptom scores and asthma control when compared with BDP and formoterol administered via separate inhalers.[7,13]
- Comparable efficacy in improving lung function outcomes (PEF, FEV_1) when compared with other ICS/LABA fixed combinations, using lower equivalent doses of BDP.[11,12,13]
- Significantly higher levels of asthma control, better quality of life and the use of lower daily ICS doses when compared with large particle ICS/LABA pMDIs as demonstrated in real-life studies.[8]
- Improved safety and tolerability profile due to lower systemic absorption and a reduction in the amount of ICS deposited in the oropharynx.[10]

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