An overview of the clinical efficacy of HFA-BDP in asthma

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Introduction

The replacement of chlorofluorocarbon (CFC) propellants with hydrofluoroalkane-134a (HFA), and the introduction of a pressurized metered dose inhaler (pMDI) in the recent reformulation of beclomethasone dipropionate (BDP), has resulted in a product with aerosol particles of a smaller mean mass aerodynamic diameter (MMAD) than conventional CFC-BDP MDIs (1,2).

The purpose of the current report is to present data showing that this new formulation of HFA-BDP (QVAR™, 3M Pharmaceuticals, St Paul, MN, U.S.A.) is at least as effective in alleviating the symptoms of asthma as conventional CFC-BDP inhalers, when used at a significantly lower dose. To support this assumption, data comparing the new HFA-BDP formulation with conventional CFC-BDP formulations is presented, namely: patterns of inhaled corticosteroid (ICS) distribution in the oropharynx and lungs; efficacy/potency ratios as measured by pharmacodynamic analysis; the clinical effect of switching from a CFC BDP to a half dose of HFA BDP, and the efficacy of long-term use of HFA-BDP in patients with moderate asthma.

HFA-BDP

HFA-BDP is a completely new preparation of BDP, which has been recently formulated to meet CFC-free requirements. To accommodate the new formulation, which, unlike CFC-MDIs, is a solution rather than a suspension of drug in propellant, different parts of the inhaler, including the valve (elastomers, seals and gasket) have been modified. In addition, to optimize ICS deposition in the airways, the actuator has been redesigned.

The deposition pattern of BDP particles in the lungs is a function of several factors, including respiratory tract geometry, airflow, particle diameter and density, and the time spent in the airways during breath-holding. Particles are distributed in the airways according to their MMAD, smaller particles more effectively penetrating the more distal regions of the lung: upper airways (MMAD = 3 µm); main bronchi (MMAD = 2 µm); peripheral airways (MMAD = 1.5 µm); more distal airways (MMAD = 0.5 µm).

Efficacy/potency ratio

By improving drug delivery to the airways, the new HFA-BDP formulation should also enhance respiratory function. To test this assumption, a protocol was designed to compare CFC-BDP with HFA-BDP in over 300 patients with moderate asthma who required regular use of ICS. In this multicentre, randomized, parallel group, blinded study, following a run-in period of 7 to 14 days (during which time the patients continued to receive their usual ICS medication), the patients entered an ICS washout period during which dependence on ICS to maintain asthma control was established. Subsequently, patients were randomized to

![Fig. 1. Particle size distribution of BDP in CFC suspension and HFA solution. --- CON-BDP; --- HFA-BDP.](image-url)
Relative dose ratio 3.2
(95% CI 11.3–15.8)

Relative dose ratio 2.6
(95% CI 11.1–11.6)

change from baseline in FEF$_{25-75\%}$ at week 6 (Fig. 4) concluded that there was a shift to the left for HFA-BDP compared to CFC-BDP. Using these data, a dose-comparison relationship indicates that it would take 2.6 and 3.2 times the dose of CFC-BDP (compared to HFA-BDP) to obtain the same improvement in FEV$_1$ and FEF$_{25-75\%}$, respectively, as predicted for HFA-BDP.

The effects of switching from a conventional CFC-BDP to an HFA-BDP at a ratio of 2.5:1

To further confirm the potency ratio between HFA-BDP and conventional CFC-BDPs a total of 149 patients were included in a double-blind, double-dummy, parallel-group, multicentre, randomized study, which compared the efficacy of HFA-BDP 400 µg day$^{-1}$ vs. CFC-BDP 1000 µg day$^{-1}$ over a 10-week period in patients with moderate asthma (7). Prior to randomization, all patients received CFC-BDP 1000 µg day$^{-1}$ during a 4-week run-in period. No significant difference in symptom scores and pulmonary function parameters [morning peak expiratory flow (AM PEF), FEV$_1$, and PC$_{20}$FEV$_1$] was recorded between the two groups at the end of treatment (Fig. 5), indicating that HFA-BDP 400 µg day$^{-1}$ provides an equivalent control of asthma symptoms to CFC-BDP 1000 µg day$^{-1}$. This result confirms the prediction of a 2.5:1 potency ratio between the two formulations.

Long-term maintenance of asthma control

The long-term efficacy of HFA-BDP (200–800 µg day$^{-1}$) was compared to CFC-BDP (400–1600 µg day$^{-1}$) in a
randomized prospective study of 12-months' duration (8). Patients participating in the study had a ≥6 month history of asthma and were receiving CFC-BDP 400–1600 µg·day⁻¹. Patients were randomized to the same dose of CFC-BDP (n = 119) or to approximately half the dose of HFA-BDP (n = 354). The study clearly demonstrated that asthma control was maintained during the 12 months of treatment following the switch from CFC-BDP to half the dose of HFA-BDP. In addition, there was no significant difference between the time to onset of acute exacerbations or increased asthma symptoms (Fig. 6) (9). Finally, the long term Juniper overall Quality of Life score (10), was significantly higher in the HFA-BDP group after 12 months of treatment (Fig. 7) (8).
Conclusion

In conclusion, compared to conventional CFC-BDP formulations, the new HFA-BDP formulation improves drug deposition in the lungs while reducing oropharyngeal deposition. The resulting greater efficacy of the new formulation is proportional to the efficiency of lung delivery, which is a result of improvements in the design of the inhalation device and the use of HFA 134 as a propellant. Other advantages of the new formulation include lower dosage requirements (2–2·5:1 dose ratio) and an effective long-term maintenance of asthma control with clear patient benefits in quality of life.

References

7. Magnusen H. In moderate asthma (400 µg day⁻¹) beclomethasone dipropionate (BDP) delivered by metered dose inhaler (MDI) with HFA-134a propellant is as effective as 1000 µg day⁻¹ BDP inhaled from MDI containing CFC. Eur Respir J 1998; 12 (Suppl. 28): 61s.