Dear Editor

Equivalence of hydrofluoroalkane (HFA) and chlorofluorocarbons (CFC) formulations of inhaled beclomethasone

We read with interest the recent article of Milanowski et al. (1) which reported an apparent equivalent anti-asthmatic effect of low (400 μg per day) and high (2000 μg per day) doses of HFA-134a (Norton Healthcare Ltd, London, U.K.) and CFC formulations of beclomethasone dipropionate (BDP). In order to evaluate the relative potency of two inhaled corticosteroid formulations, it is necessary to compare anti-asthmatic effects on the steep part of the dose-response curve, preferably using at least three doses (2). In the study of Milanowski et al. baseline values for mean forced expiratory volume in 1 sec (FEV1) showed that both groups were well matched for the low dose study (67% predicted) and the high dose study (70% predicted). The primary efficacy variable from the intent-to-treat population showed no evidence of a dose-response effect between 2000 μg per day and 400 μg per day for either the CFC or HFA formulations, in terms of the change in FEV1 between baseline and end-point after 6 weeks of treatment. For HFA-BDP the mean change in FEV1 was 0.41 at 400 μg and 0.21 for 2000 μg, whilst for CFC-BDP values were 0.31 and 0.31, respectively. In other words, for the patients who were studied, 400 μg day⁻¹ of either CFC or HFA-BDP was on the plateau part of the dose-response curve. Hence it is not possible to make any valid conclusions regarding therapeutic equivalence from these data.

Had the authors evaluated doses of BDP less than 400 μg per day on the steep part of the dose-response curve, it is conceivable that differences in anti-asthmatic potency between the two formulations may have become evident. In this respect we have recently performed a pharmacokinetic study to compare the systematic bioequivalence of a 1000 μg nominal dose of HFA-134a BDP metered dose inhaler (as Beclazone-CFC free 250 μg per actuation, Norton-Waterford, Ireland) or CFC containing metered dose inhaler (Beclazone 250 μg per actuation) (3). The HFA-134a BDP inhaler was identical to that used in the study of Milanowski et al. Plasma levels of beclomethasone-17-monopropionate (17-BMP) were measured over a 12 h period after inhalation. The results showed mean values for the area under the curve (AUC₀⁻¹²) were 1.5 fold greater, and mean values for maximum plasma concentration (C_max) were 1.9 fold greater when comparing HFA-BDP vs. CFC-BDP formulations. Furthermore, the 90% confidence interval for the ratio of HFA-BDP to CFC-BDP was outside of that established for bioequivalence for both AUC (90% CI 1.33–1.95) and C_max (90% CI 1.57–2.61).

These pharmacokinetic data would therefore suggest that the HFA and CFC formulations of BDP are not bioequivalent. Indeed, this has been shown with another HFA-134a formulation of BDP metered dose inhaler (3M Healthcare Limited, Loughborough, U.K.) where the relative dose ratio for potency for HFA-BDP versus CFC-BDP was 2.6, as assessed by comparing effects on the steep part of the dose-response curve FEV1 in patients with moderate to severe asthma (4). Caution should therefore be exercised in interpreting the data of Milanowski et al. in terms of making recommendations for directly substituting HFA (Norton Healthcare) for CFC formulations of BDP metered dose inhaler on a micromgram equivalent basis. Properly designed clinical trials using a dose-response comparison are required in order to provide more rational dosing recommendations when switching between the two products.

B. J. LIPWORTH AND C. M. JACKSON
Department of Clinical Pharmacology, Ninewells Hospital and Medical School, University of Dundee DD1 9SY, Scotland U.K.

References

Dear Editor

Is inhaled beclomethasone (BDP) with a non-CFC propellant equivalent to the CFC propellant formulations?

The reformulation of beclomethasone dipropionate (BDP) metered dose inhalers (MDIs), using hydrofluoroalkane (HFA) propellants to replace chlorofluorocarbons (CFC) is
challenging. At present one product is available in the U.K. (QVAR-3M Pharmaceuticals) and a generic version is described in the studies of Milanowski et al. (1). Most MDI preparations are a suspension of drug particles. However a BDP suspension in an HFA propellant is difficult to achieve. Some manufacturers have solved this problem by using an solvent (ethanol), in combination with HFA propellant, to produce a solution aerosol. Although not yet reported in the literature the indications are that pharmaceutically there is little difference between QVAR and the generic HFA MDI formulation of BDP (Norton Healthcare Ltd, U.K.) used by Milanowski et al. (1). There is also a lack of pharmacokinetic data to provide indications about the systemic delivery for the generic HFA BDP aerosol. Clinical studies comparing QVAR to CFC BDP MDIs have shown that the dose could be halved (2,3) but others have shown dose comparability (4,5). The report by Milanowski et al. (1), like the previous studies (2–5), was not designed to be able to make firm recommendations about the clinical dose.

The BDP particles emitted from solution aerosols are much smaller than conventional MDI suspensions. It has been quoted that the majority of the particles in the respirable fraction of QVAR are <2μm compared with 1–6 μm for the BDP CFC MDIs (6). The effect of inhaling such small particles may be to increase lung deposition with potentially increased delivery to the alveoli (7). If lung deposition of BDP to the lungs, especially the peripheral zones, is increased and the amount swallowed is decreased then there will be a significant increase in the systemic availability. Pharmacokinetic studies in adults have shown that 200 μg of BDP from an HFA MDI (QVAR) delivers 13.4% more to the systemic circulation than 400 μg from the CFC MDI formulations of BDP (8). This data shows that, in adults, if comparable doses would have have used the total systemic delivery of drug from the HFA BDP aerosol would be 2.27 times more than a CFC MDI. A recent study in children (aged 10–14 years) indicates that the breath-actuated version of this BDP HFA MDI delivers 2.75 times more drug to the systemic circulation as a CFC MDI attached to a large volume spacer (9).

Dosage reductions due to increased systemic availability, from these new MDI formulations, are essential because inhaled corticosteroids are associated with dose-related systemic adverse effects (10). This relationship is exponential in nature with a greater effect as the dose is increased. The dose response relationship for the clinical effect is exactly the opposite and less pronounced. There is a relatively flat nature to the dose-response curve for lung function parameters within the therapeutic dosage range for inhaled corticosteroids (11,12).

Milanowski et al. (1) have reported the results from two parallel group studies. The 'low' dose parallel group study involved steroid naïve asthmatics with a baseline mean forced expiratory volume in 1 sec (FEV1)% predicted of about 67% for the HFA and CFC preparations. The BDP doses were 400 μg per day and the mean increase in FEV1 was 0.3 and 0.4 l respectively. The high dose parallel group study involved asthmatics inhaling 800–2000 μg BDP per day prior to study entry. All received 2000 μg BDP per day as the HFA or CFC aerosol. Baseline data were similar to the low dose study with a mean FEV1% predicted of 70%. The mean increase in FEV1 was 0.3 and 0.2 l respectively. All these results may have been maximal responses at the plateau of the dose response relationship.

The concluding statement by Milanowski et al. (1) that patients may be switched directly from their existing CFC-formulated BDP MD1 to the generic cannot be made. This study (1), like many previous studies was under-powered to provide positive evidence of equivalence using the normal method of non-overlapping 90% confidence intervals. It is also important to study comparative efficacy of doses on the steep part of the dose response curve in order to make true comparisons. The study reported by Busse et al. (5) indicates a dose response relationship for BDP using HFA and the CFC MDIs but the response is fairly flat due to the large doses used. Therefore for their the outcome data they have used a Finney’s Bioassay to show the HFA formulation was 2.6 times more potent than the CFC version. However the 95% confidence interval for this value was 1.1–1.1 and thus on this basis the greater potency (to show a marginally better response in the FEV1) may not proven with respect to clinical management.

Seamless transition is only possible if the amounts deposited in the lungs and delivered to the systemic circulation are the same and when the patient notices little difference in taste and the emitted plume. The switch to HFA aerosols seems to have turned into a race to be first rather than a quest to produce preparations which enable seamless transition. This represents a threat to the management of stable asthma patients. The generic BDP HFA aerosol used by Milanowski et al. (1) has been licensed in some countries as a dose for dose swap for the CFC formulation. For QVAR the recommendation is to halve the dose for well-controlled patients. If both were available in a single country with different dosage recommendations then problems will be created when a prescription for a beclomethasone HFA metered dose inhaler is presented for dispensing. In the future the availability of a new formulation which ensures seamless transition between CFC and HFA beclomethasone aerosols will now create more confusion.

H. CHRYSTYN
Pharmacy Practice, The School of Pharmacy, University of Bradford, Bradford, BD7 1DP, U.K.

References


Indeed, the focus of the high dose study (2000 μg day−1) was primarily on demonstrating comparable safety and tolerability of BDP-HFA and BDP-CFC, while the lower dose study was designed to evaluate efficacy and safety in patients not currently maintained on inhaled steroids. This showed significant and equivalent improvement in lung function and asthma symptoms with both treatments. Moreover, the lung function responses seen in the Milanowski et al., studies are in keeping with responses seen in other published studies of high dose inhaled corticosteroids (1,2). We would dispute the point by Chrystyn concerning the studies being under-powered to provide evidence of equivalence since both were planned with full statistical considerations in determining detection of any clinically relevant differences between the hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC) products.

The issue of assessing efficacy at low doses has in fact already been addressed in another 12 week study in 200 asthmatic children with a beclomethasone dipropionate (BDP) dose of 100 μg b.d., using similar formulations of CFC and CFC-free BDP to those used in the adult asthmatic study by Milanowski et al., 1999. This paediatric study has also shown significant mean improvements in PEF for both BDP-CFC and BDP-HFA that were within 3% of each other at endpoint (95% CI 99-1, 106-2%), with similar equivalence in other efficacy and tolerability parameters. It is intended that these data be published in due course.

Thus therapeutic equivalence of these BDP-HFA and BDP-CFC formulations (Norton Healthcare Ltd, U.K.) has now been demonstrated across a wide dose range in patients with all severities of asthma.

The pharmacokinetic data of Lipworth and Jackson and the hypothetical lung deposition referred to by Chrystyn, although interesting, are not necessarily reflected in clinical practice in terms of asthma control. Caution must be exercised when interpreting systemic steroid absorption from both swallowed and inhaled drug. It is not stated whether their data were acquired from healthy volunteers or patients with asthma, but it is likely that the ratios of plasma beclomethasone-17 monopropionate from inhaled BDP-CFC and BDP-HFA will vary between subjects and also across doses, as well as with inhaler technique. Taking an arbitrary mean dose ratio from pharmacokinetic data based on systemic absorption and then switching patients to a lower inhaled dose of BDP-HFA when changing from BDP-CFC exposes some patients to a risk of undertreatment and possible asthma exacerbation. Based on the evidence from our own studies, where the aim was to evaluate therapeutic equivalence, it is not only justified, but would appear far simpler and less risky, as well as being more convenient for asthma sufferers and health professionals, to switch patients on a 1:1 basis when changing from BDP-CFC to BDP-HFA. Doses can later be titrated down on an individual basis in a manner consistent with good current practice (e.g. BTS guidelines). As to the potential for the HFA product to result in a less favourable safety profile, this has not been the case with BDP-HFA in these studies nor in the post-marketing experience with this

Response to letters from Dr B.J.
Lipworth, Dr C.M. Jackson and Prof. H. Chrystyn re: paper by Milanowski et al. (Respir Med 1999; 93: 245–251)

We would like to thank Dr Lipworth and Prof. Chrystyn for their interest and comments, which point to a number of important issues in the design of inhaled corticosteroid trials and their application to asthma treatment. They are quite correct in pointing to the difficulty of demonstrating relative potency of inhaled corticosteroids at high doses and the importance of assessing equivalence also at low doses.