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Letters to the Editor

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 (FEV_1) 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 populations 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 FEV_1 between baseline and end-point after 6 weeks of treatment. For HFA-BDP the mean change in FEV_1 was 0·41 at 400 μg and 0·2 l for 2000 μg, whilst for CFC-BDP values were 0·3 l and 0·3 l, 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 (AUC_{0-12}) 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 FEV_1 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 microgram 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.

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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

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