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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. Indeed, the focus of the high dose study (2000 $\mu g\,day^{-1}$) 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 under-treatment 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

product in Ireland. Following its launch in February 1998, we estimate in excess of 10000 patient years experience has been gained without any untoward experiences being reported. This represents the greatest cumulative experience obtained to date for any BDP-HFA product and is arguably the strongest and most meaningful evaluation of such a product.

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Re: inhaled beclomethasone (BDP) with non-CFC propellent (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma (*Respir Med* 1999; 93:245–251)

In this journal Milanowski and co-workers published their results of an equivalence trial comparing a HFA- and CFC-BDP formulation (1). Their intention was to show that the recently developed HFA-formulation is equivalent to the older CFC one. The conclusion was that both formulations were equivalent and a 'change-over of patients straightforward'. A number of reasons render this conclusion of equivalence, however, questionable.

This study based the equivalence claim on reporting a lack of statistically significant differences between two preparations. This approach has become known as the so-called power approach. In this approach, *a priori*, one defines a maximal allowable difference between the two preparations. Subsequently one calculates a sample size enabling the researcher to find that difference. When the study evaluation does not report any significant differences, the actual difference between the two preparations must have been smaller than the predefined critical (and detectable) one. The conclusion therefore is that the actual difference between the two is smaller that the critical one and equivalence can be claimed. However, the sample size calculation (which is pivotal) is always based on retrospective data (mean and standard deviation), while these data can differ from the actual in the selective sample. So it is possible that the standard deviation in the sample is larger than in the retrospective data. When that happens, the study will by definition result in no significant differences: the study is under-powered due to the larger standard deviation (2).

When we follow this approach based on the data of the low dose study in Table 3 of the publication, we can read a mean FEV_1 of $2{\cdot}5 \pm 0{\cdot}8$ l for the reference CFC-BDP formulation. So with an acceptable difference of 0·2 l, the lowest test HFA-BDP may be 2·3 l. Sample size calculation with a standard deviation of 0·8 gives us a size per group of 338. A standard deviation of 0·305, together with the other data, would lead to the cited sample size of 50 per group. We therefore ask ourselves whether this study was under-powered and could not but result in non-significant differences, due to an incorrect estimate of the standard deviation.

The power approach was put out of use much for the above reason. The current approach of the two one-sided *t*-test does not suffer from the drawback of under-powered studies. It is designed in such a way that an under-powered study always leads to a conclusion of inequivalence. This approach is based on a null hypothesis of inequivalence and an alternative one of equivalence. To claim equivalence one must reject inequivalence, which in statistical terms means 'significant differences'. It is easy to see that under-powered study will never be able to reject the null hypothesis of inequivalence. A study must be sufficiently large to reject inequivalence and accept equivalence. In this way it is impossible to market inequivalent preparations as result of a flawed power approach study. The patient risk to use inequivalent product is significantly reduced after implementation of the two one-sided *t*-test.

Now following the two one sided *t*-test approach and again assuming that the maximal allowable difference is 0·2 l, the difference between the two preparations is 0·1 l with a standard deviation of 0.8, the sample size per group would be 1097!

The next point is the choice of a FEV_1 difference of 0·2 l as the maximal allowable difference. The authors thereby state that the mean FEV_1 in the HFA-group could be $2{\cdot}5 - 0{\cdot}2 = 2{\cdot}3$ l and still be acceptable. A value lower than 2·3 l however would mean that the improvement in that group would be very low: an increase from 2·2 to 2·3 l would be sufficient to claim non-significant differences. In other words, while the CFC-group improved 0·3, an improvement of a mere 0·1 l in the HFA-group would be sufficient to claim equivalence. We feel that such a large difference between the improvements is not acceptable.

To conclude we feel that the approach taken by the authors does not allow the conclusion of equivalence and would ask them to elaborate on the starting points of their sample size calculations.

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