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Reply to Drs Seale and Donnelly

Drs Seale and Donnelly should provide a dose-range context for each of the currently used inhaled steroids rather than focusing on their study which contrasts high-dose FP with BUD. It is important to underscore the starting dose of each compound, since the majority of asthmatics with mild/moderate asthma will experience minimal (and not clinically significant) HPA axis suppression at these recommended doses.

The authors cite their own study (their ref. 11) that 'a more potent inhaled corticosteroid ... is insufficient to materially improve the topical-to-systemic ratio', hence, the issue of corticosteroids is at the 'crossroads'. However, their investigation was not an efficacy study but merely showed the *expected* cortisol suppression at the high-dose ranges of the two compounds studied. They also fail to cite the important study of Noonan where high-dose FP allowed discontinuation of systemic prednisone, clearly an improvement for each of those patients in the topical-to-systemic ratio.

Their own study that they cite as evidence for failure of a new steroid (FP) to achieve a higher topical-to-systemic ratio has clear-cut limitations. This study was performed in normal subjects, not asthmatics, as they acknowledge in the Discussion. The modest reductions in cortisol profiling at the lower doses (800 μg of BUD; 750 μg of FP – not 500 μg, an error in the manuscript) is not 'surprising' but, in fact, is expected. These doses are known to reduce cortisol levels as that fraction of the inhaled dose that is inhaled into the lung (approximately 20% for most compounds) is ultimately systemically absorbed. Clearly what needs to be accomplished is the establishment of bioequivalent dosing for each of the inhaled steroids (using the HPA axis as the marker of *systemic* bioavailability) over broad (low, medium, high) dose ranging. With this information, each compound could then be compared to the others at bioequivalent dosing in *efficacy* trials to see if the unique properties of a compound favourably alters the efficacy profile.

Finally, it is possible that other tissues and biological end points (e.g. growth in children) are even more sensitive markers of glucocorticoid 'toxicity' than the HPA axis. Nevertheless, it is likely that glucocorticoid exposure at high dosage, regardless of route of administration, over prolonged periods will carry risk. In such patients, it is likely that systemic steroids carry an even greater risk due to the adverse topical-to-systemic ratio.

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Reply to Drs Seale and Donnelly

Issues about the safety of inhaled corticosteroids and the relative efficacy to safety ratio of different inhaled steroids are of considerable clinical importance. I do not think Drs Seale and Donnelly's letter or the paper by Donnelly *et al.* (their ref. 11) which triggered this letter contribute much in this regard. Efficacy and safety mean very little in isolation; when considering an inhaled corticosteroid one needs to consider the ratio of efficacy to safety as the authors point out. Information from studies such as Donnelly *et al.* provides information of very limited value when performed in normal volunteers with no measures of efficacy. It is clear from studies with inhaled fluticasone, β_2-agonists and diosodium cromoglycate that normal subjects absorb far more inhaled drugs from their lungs than asthmatic subjects and thus normal volunteer studies will always overestimate the side-effects of inhaled steroids. It is disappointing that the authors do not address this fundamental problem. It could be argued that for the ratio of side-effects of FP to BUD the fact that it is done in normal subjects is irrelevant because although the decriment in cortisol will be less in the asthmatic subjects, the ratio would remain the same. However, this is not likely to be the case as different particle characteristics of the two inhalers may mean that they behave quite differently in the asthmatics to the normal subjects. In discussing previous studies the authors completely ignore a large number of studies which have the tremendous advantage of using inhaled steroids at the doses which would be appropriate for that patient's asthma severity and measuring efficacy and safety within the same study. These studies, which were done in a far larger number of patients than the small-normal volunteer studies, give a quite different result. Ayres *et al.* compared FP 1 and 2 mg with budesonide 1·6 mg both in terms of efficacy and safety. The order of efficacy was budesonide 1·6 mg, FP 1 mg, FP 2 mg and the order of the cortisol was FP 1 mg, budesonide 1·6 mg, FP 2 mg. This is consistent with an efficacy ratio of approximately 2:1 with no evidence for increased side-effects and runs counter to the authors' argument that there is a 3:1 ratio in terms of systemic side-effects. Ringdal *et al.* also showed greater efficacy of FP despite being used at half the dose of budesonide with slightly less effects on adrenocortical