Corticosteroid treatment of asthma: now at the crossroads

Anti-inflammatory corticosteroids have enjoyed a central role in the treatment of asthma for almost half a century; oral cortisone was first used in 1950 with good effect (1). Subsequent clinical trials revealed that corticosteroids were useful for treating exacerbations of asthma (2) and prednisone became the standard long-term treatment for patients with troublesome persistent symptoms. The typical side-effects associated with long-term oral treatment were traded off against the obvious benefits associated with better control of the asthma.

The next major development came in 1972 (3), with the introduction of the inhaled corticosteroid, beclomethasone dipropionate (BDP), which became widely accepted standard therapy for patients whose asthma was inadequately controlled with bronchodilators. Initially the recommended doses were fairly modest (400-1000 µg day\(^{-1}\)), but with favourable clinical experience the tendency (particularly in the U.K. and Australia) was to gradually increase the dosage (4), sometimes reaching 2000 µg day\(^{-1}\) or more in patients whose asthma was particularly difficult to control.

As evidence accumulated that asthma is primarily an inflammatory disorder, it seemed rational to use inhaled corticosteroids to treat the underlying disorder. The enormous benefits of these drugs were quickly acknowledged, and at the time there was some justification for believing that the inhaled route of delivery would avoid significant systemic absorption provided the dose of BDP was below 2000 µg daily (5). When BDP first became available for clinical use laboratory assays for measuring drug concentrations in plasma were not very sensitive, but with the recent advent of gas chromatography–mass spectrometry (GC–MS) it is now possible to quantify anti-inflammatory corticosteroids in plasma after inhalation of doses that are well within the recommended therapeutic range (6). Moreover, evidence that systemic drug absorption is sufficient to cause adverse effects has come from case reports in which Cushingoid features have developed in patients taking high-dose inhaled corticosteroids (7).

In recent years, structural modifications of the corticosteroid molecule have led to newer inhaled corticosteroids such as budesonide (BUD) and fluticasone propionate (FP), which are subject to greater first-pass hepatic metabolism, i.e., they have lower oral bioavailability. These kinetic differences reduce the contribution to overall systemic absorption from that part of the dose which is inadvertently swallowed during administration of inhaled corticosteroid. However, although FP is inactivated extensively (99%) by first-pass hepatic metabolism (8), there is still significant systemic activity when it is given by inhalation in large doses (9). This observation highlights the fact that the lung is a very efficient route for systemic delivery of inhaled corticosteroids and that gastrointestinal absorption of drug that is swallowed rather than inhaled makes only a minor contribution to the total systemic bioavailability of an inhaled corticosteroid.

Initial clinical studies with FP suggested that the strategy of structural modification of the steroid molecule may have yielded an inhaled corticosteroid with greater topical potency and less systemic activity than BDP or BUD (10). However, this attractive possibility overlooked some important weaknesses in the design of preliminary studies which had underestimated the difficulty in calculating relative dose potency ratios for efficacy and systemic activity for different corticosteroids when most study designs had included only one or two doses of each drug. Reliable dose potency ratios for comparison of drugs within the same class can only be obtained from studies that include multiple doses across the full dose-response range and make appropriate adjustments for placebo effects and diurnal changes in pulmonary function and cortisol production.

A recently published randomized placebo-controlled trial of the two newest inhaled corticosteroids (BUD and FP) involved administration of multiple doses of each of these drugs to 28 normal volunteers in a seven-way cross-over design (11). Repeated blood samples for measurement of plasma cortisol were taken over a 24-h period to determine the area under the curve (AUC\(_{24}\)) after 4 days of treatment with each of three doses of BUD and three doses of FP. The surprising finding was that even modest doses of BUD and FP, which equate to those routinely prescribed for many patients with asthma (800 mcg d\(^{-1}\) budesonide and 500 mcg d\(^{-1}\) fluticasone), caused a discernible reduction in plasma cortisol AUC\(_{24}\). In addition, dose-response analysis showed that, on a microgram-for-microgram nominal dose basis, the potency ratio for the systemic activity of FP relative to BUD was 3:1, which marginally exceeds the reported efficacy ratio of approximately 2:1 (10).

This leaves us with the disappointing impression that development of a more potent inhaled corticosteroid by molecular structural modification is insufficient to materially improve the topical-to-systemic activity ratio, which relates clinically to the overall risk-benefit profile, mainly because the lung is such an efficient route for systemic drug delivery.

The advent of anti-leukotriene drugs, the first of which (montelukast, zafirlukast and zileuton) are now available, offers an alternative novel approach to the long-term treatment of the underlying inflammation of asthma (12). Whilst it has been usual practice in the past to develop
inhaled formulations of anti-asthma drugs to direct them to the site of action, many pharmaceutical companies have elected to develop the initial anti-leukotriene drugs as oral formulations, presumably because of patient preference with this route of administration in the large U.S. and Japanese markets. The availability of this new class of anti-leukotriene drugs should prompt the pharmaceutical industry to escalate its efforts to discover topically active corticosteroids which have minimal systemic effect, either by intensified endeavours in medicinal chemistry or by some alteration to the pharmaceutical formulation such that the effects of the inhaled drug are confined to the lung.

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References


Reply to Drs Seale and Donnelly

Drs Seale and Donnelly make several important points regarding the challenge inhaled glucocorticoids now face with the introduction of leukotriene modifiers (1). However, it is the opinion leaders who are at the crossroads and face the challenge in defining the appropriate management for asthma. In recent years, opinion leader teams or ‘expert panels’ have profiled inhaled glucocorticoids as the ‘preferred’ long-term asthma control medication (2,3). Numerous studies show that inhaled glucocorticoids improve overall asthma management, reduce the need for rescue bronchodilator therapy, and reduce hospitalizations (4-7). They also improve pulmonary function and reduce airways hyperresponsiveness with long-term treatment (4-5). Recent observations suggest that the response to inhaled glucocorticoids is highly dependent on the time of intervention, the earlier used the better (5,7-9). These observations have raised the question whether delays in intervention, specifically with inhaled glucocorticoids, lead to irreversible or incompletely reversible changes in airway pathology.

The inhaled glucocorticoids as a class, however, face a formidable challenge to retain their position as the preferred medication for long-term asthma control. Their effect is limited to the duration of treatment (5), they do not induce remission, and the response to glucocorticoids can vary among patients (10). In addition, recent reports have raised concern regarding the risk of adverse effects with long-term high-dose inhaled glucocorticoid therapy (11,12). Attempts to compare the various inhaled glucocorticoids have placed emphasis on measures of cortisol suppression and have consequently drawn attention to the systemic effects of all inhaled glucocorticoids. Indeed, Seale and Donnelly’s report utilizes cortisol suppression to derive potency ratios for the systemic effect of two inhaled glucocorticoids (1). Unfortunately, this type of information has not defined a ‘preferred’ inhaled glucocorticoid. It appears that as the potency of an inhaled glucocorticoid increases in relation to efficacy, there appears to be a corresponding increase in potency on cortisol suppression. Putting the two measures together, that is, efficacy and systemic effect potency, could lead to the development of a therapeutic index. Attempts to define this therapeutic index have not been successful, but studies are now in progress under the direction of the National Heart, Lung and Blood Institute Asthma Clinical Research Network.

Other medications described as ‘controllers’ prevent symptoms and improve pulmonary function, but do not resolve airways inflammation, for example long-acting β-agonists. Interest has grown in the leukotriene modifier class of long-term asthma controllers. In the U.S.A., three