

How should inhaled glucocorticoids be compared?

Inhaled glucocorticoids are firmly established as effective therapy for chronic asthma. Despite a long history in the management of asthma, a number of important questions regarding their use remain. The study by Agertoft and Pedersen¹ points out a number of these key points, as well as the difficulties encountered when attempting to compare the various inhaled glucocorticoids with one another. Comparing inhaled glucocorticoids has become particularly important because new agents (with higher potency claims) have been or will be introduced in the near future (along with novel inhaled drug delivery systems) and because pharmaceutical firms compete for the position of maker of the inhaled glucocorticoid of choice. Recently published asthma treatment guidelines, the Global Initiative for Asthma, do not distinguish among inhaled glucocorticoids.² Rather, the available inhaled glucocorticoids are assumed to be equivalent in terms of their antiinflammatory activity on the basis of present data.² Revised National Institutes of Health guidelines, however, will suggest that some inhaled glucocorticoids are more potent than others, with very limited evidence.

COMPARING EFFICACY

How should the efficacy of inhaled glucocorticoids be compared? Although there are several potential models available for these comparisons, there is no single model that completely answers the question of how inhaled glucocorticoids equate with one another. Comparative efficacy studies can be of parallel design or of cross-over design, which have difficulty controlling for the potential effect of the duration of treatment. Inhaled glucocorticoids can also be compared in terms of their ability to allow for oral steroid dose reduction, which is an entirely different indicator of effectiveness. The therapeutic end point studied, whether it is symptoms, pulmonary function, or other parameters, may respond at different rates, further complicating any comparisons of inhaled glucocorticoids.

Other factors that can affect how inhaled glucocorticoids demonstrate efficacy are the patient population

(e.g., severity of disease, children vs adults), concomitant medications and prior glucocorticoid therapy allowed, and possible seasonal variability of asthma symptoms. These are in addition to the difficulties encountered when treating a chronic disease with drugs that have equivocal dose-response relationships, the efficacy of which can be affected by the duration, frequency, and timing of administration. Duration of symptoms before initiation of therapy may also influence the efficacy observed. This latter point remains controversial, but recent reports suggest that if the duration of asthma symptoms before administration of inhaled glucocorticoids is initiated is prolonged, the response to treatment can be diminished.³⁻⁵

An important but often overlooked point is that when control of asthma symptoms is studied, the *minimum* required doses of inhaled glucocorticoids must be compared. As discussed by Agertoft and Pedersen,¹ equal control of symptoms while patients are receiving different doses of inhaled glucocorticoids (e.g., X μ g/day of glucocorticoid A and 2X μ g/day of glucocorticoid B), as shown in numerous one-on-one comparative studies, does not necessarily demonstrate that glucocorticoid A is twice as potent as glucocorticoid B. Similarly, if glucocorticoid C provides better efficacy than glucocorticoid D at the same dose, it is difficult to quantify any superior potency or effectiveness of glucocorticoid C.

Agertoft and Pedersen¹ also point out the importance of the method of drug delivery in the analysis. For example, it is well known that the Turbuhaler device delivers twice as much drug to the airways and lungs as a metered-dose inhaler,⁶ and this difference in delivery can alter the apparent efficacy of budesonide.⁷ Other dry powder inhalers have not been as extensively studied; however, it is believed that Rotahaler and Diskhaler result in bioavailability comparable to that of metered-dose inhalers.⁸ In the study by Agertoft and Pedersen,¹ equal efficacy was observed between budesonide Turbuhaler and fluticasone propionate Diskhaler, leading the investigators to conclude that the two drug-inhaler combinations provide similar efficacy.¹ As stated, the implication of this conclusion, assuming that lung deposition of the administered drug after inhalation from Turbuhaler is greater than that achieved with Diskhaler (and therefore more drug is available to exert its effect), is that fluticasone propionate is inherently more potent than budesonide, which is consistent with its manufacturer's claims.

COMPARING SAFETY

Comparative safety of inhaled glucocorticoids, specifically their risk for systemic adverse effects, is another

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important and unanswered question. Agertoft and Pedersen,¹ however, point out that safety of a given inhaled glucocorticoid must be considered with regard to its efficacy. Many studies have simply compared the risk for systemic effects from comparable doses of inhaled glucocorticoids; however, these may not be ideal because there is no assessment of efficacy of such doses in the treatment of asthma. The difficulty is that although normal, nonasthmatic volunteers may not be the appropriate population in which to conduct such studies, steroid-naïve asthmatic subjects (with an adequate level of asthma severity) are difficult to identify and recruit.

What safety parameters should be compared between the different inhaled glucocorticoids? Certainly, systemic effects such as growth (in children), adrenal suppression, and bone metabolism are important clinical measures; but glucocorticoids have numerous other systemic adverse effects.⁹ When investigating systemic effects of inhaled glucocorticoids, several important questions must be answered.

1. Is the patient population appropriate?
2. Is the sample size adequate?
3. Have controls for the effects of prior glucocorticoids (including oral) been applied?
4. Does the test have adequate sensitivity and specificity?
5. Are observed statistically significant differences *clinically* significant?
6. Do observed short-term changes predict long-term adverse effects?

The two final questions are probably the most important but are not often addressed.

With regard to the effects of inhaled glucocorticoids on growth, a relatively new technique called *knemometry* has emerged in recent years. This is a method that can detect very small changes in lower leg growth. With the use of knemometry, a number of studies have demonstrated that inhaled glucocorticoids cause reductions of lower leg growth with short-term (1-week) treatment.¹⁰⁻¹³ Unfortunately, short-term growth studies do not correlate well with long-term growth or predict final height.¹⁴ Therefore although this method may be a useful bioassay for demonstrating a systemic effect of inhaled glucocorticoids, it is not ideal for studying growth suppression. Long-term growth studies are desirable; however, the duration of pretreatment and posttreatment follow-up, patient compliance to the treatment schedule, the need to minimize concomitant therapies, the confounding effects of uncontrolled asthma and delayed onset of puberty, and the normal variations in growth patterns make these studies difficult to perform.¹⁵

Adrenal suppression resulting from inhaled glucocorticoid therapy has received a great deal of attention and remains highly controversial. Numerous studies, in which a variety of measures of adrenal function were used, have compared the systemic effects of inhaled

glucocorticoids. However, these various tests cannot be interpreted as generic markers of adrenal function because each reflects distinct aspects of hypothalamic-pituitary-adrenal axis integrity.¹⁶ Reductions in urinary free cortisol excretion, plasma cortisol concentrations, and 24-hour integrated plasma cortisol (area under the plasma concentration-time curve), which are indicative of basal adrenal function, have been shown with various doses of different inhaled glucocorticoids. These changes are to be expected, to some degree, given the augmented negative feedback and inhibition of hypothalamic corticotropin-releasing hormone in the presence of exogenous glucocorticoids.

Yet the risk for life-threatening adrenal insufficiency depends not on basal adrenal function but on the ability of the adrenal glands to produce cortisol during stress or illness.¹⁶ Indeed, vast experience with inhaled glucocorticoids would suggest that the risk for clinically relevant adrenal insufficiency is small, despite many studies demonstrating statistically significant reductions of cortisol after the administration of inhaled glucocorticoids.¹⁶ Significant adrenal dysfunction, which would warrant supplementation during periods of stress or illness, is detected by testing the adrenal response of cortisol production after synthetic adrenocorticotropic hormone administration.¹⁶

Effects of inhaled glucocorticoids on bone remodeling have also been of interest for many years. As with growth and adrenal function, studies of this adverse effect may not be examining the ideal outcome. Preferably, bone density measurements are monitored; however, by the time that bone density is significantly reduced, the risk for fractures is already increased. Investigators have subsequently turned to biochemical measures or "markers" of bone metabolism, either bone formation (such as serum osteocalcin) or bone resorption (such as urine calcium). Unfortunately, changes in these indices of bone remodeling give only an indication of the dynamics of bone metabolism and may not correlate well with reduced bone density or increased risk for fractures with long-term inhaled glucocorticoid treatment.¹⁷

CONCLUDING REMARKS

As with all medications, compliance must be assured when evaluating both the efficacy and safety of inhaled glucocorticoids. And if statistically significant differences between inhaled glucocorticoids are noted for either efficacy or safety, one must question whether the distinctions observed are *clinically* significant. Finally, pharmacoeconomic factors, such as how an inhaled glucocorticoid treatment affects use of health care resources (e.g., emergent physician visits and hospitalizations) and their costs, as well as impact on quality of life, are other meaningful comparative factors in addition to (and perhaps more importantly than) the expenses of the medications alone, which also need to be considered when inhaled glucocorticoids are compared.

With the recent introduction of fluticasone propionate, four inhaled glucocorticoids are now available in

the United States. Although inhaled glucocorticoids will undoubtedly continue to be an important weapon in the arsenal of medications for the treatment of chronic asthma, clinicians are faced with difficulty in choosing agents. A multitude of factors can affect responses to treatment and must be considered when the comparisons of inhaled glucocorticoids are interpreted. The uncertainty regarding how inhaled glucocorticoids compare with one another is also in part due to the fierce competition among the pharmaceutical companies that market the various inhaled glucocorticoids. Until further well-controlled, well-designed studies aimed to specifically address this question of equivalence are performed, the differences between the glucocorticoids and glucocorticoid-inhaler combinations and the clinical significance of such differences will remain unclear, and the confusion and conflict over which inhaled glucocorticoid might be superior will continue.

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