

Comparing inhaled glucocorticosteroids

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Inhaled glucocorticosteroids (GCSs) have a much lower potential for systemic effects than oral steroids. Nevertheless, the potential systemic effects of inhaled therapy are still an issue of concern, especially to pediatricians. Therefore, great efforts have been made to develop new GCSs with even less systemic activity for a given clinical effect. Claims are often made that some inhaled GCSs have a higher potency and/or a lower potential for systemic effects than others, but there is still much debate about the clinical importance of this and about how such possible differences should be assessed.

Both the desired and the unwanted effects of inhaled GCS therapy can be measured in many different ways, but the results of different measurements are not always in agreement. This makes the whole issue of inhaled steroid therapy complex and confusing for many clinicians. Because the prescriber of an inhaled steroid is faced with an increasingly wide range of drugs and delivery devices, it would be helpful if it were possible to calculate benefit:risk ratios for all available combinations of drug and inhaler.

This paper summarizes some of the most important factors to be considered when assessing the efficacy and safety of inhaled GCS therapy and comparing the properties of the various drug-inhaler combinations. It also highlights some pitfalls and problems associated with comparisons between inhaled GCSs in an attempt to provide the reader with a better basis for understanding some of the apparent discrepancies in results between different studies.

Which outcome should be used in the comparison?

The airway selectivity of inhaled GCSs is due to a combination of high topical corticosteroid activity and low

To cite this article:

Pedersen S. Comparing inhaled glucocorticosteroids. *Allergy* 1999; **54**, 42–50.

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ISSN 0105-4538

% of nominal dose becoming systemically available

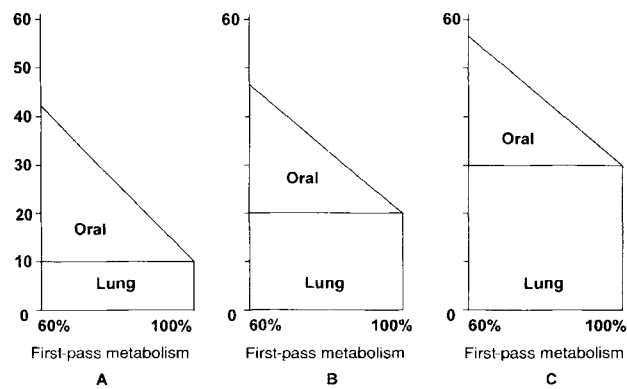


Figure 1. Systemic availability of corticosteroid delivered from three different inhalers (A, B, and C). All inhalers deliver 90% of nominal dose to patient. Inhaler A delivers 10% of nominal dose to intrapulmonary airways and 80% to oropharynx. Inhaler B delivers 20% to intrapulmonary airways and 70% to oropharynx. Inhaler C delivers 30% to intrapulmonary airways and 60% to oropharynx. Amount of systemically bioavailable drug depends upon lung deposition and upon amount absorbed from gastrointestinal tract, latter being inversely related to first-pass metabolism of drug. For given intrapulmonary deposition of drug with first-pass metabolism lower than 100%, total systemic availability of drug can be reduced by using inhaler which delivers high dose to intrapulmonary airways and/or low dose to oropharynx. These considerations may be clinically important, since differences in inhaler characteristics may result in 2–3-fold difference in drug delivery to intrapulmonary airways and even greater difference in drug deposition in oropharynx. Importance of deposition pattern increases with decreasing first-pass metabolism.

systemic bioavailability. The most relevant parameter for comparing the various inhaled GCSs, and the different formulations of a particular inhaled GCS, would therefore seem to be the *therapeutic index*: the ratio of the clinical (desired) effects to the systemic (undesired) effects of a drug/inhaler combination (Fig. 1). This is often, but not always, reflected in the ratio of the amount of topically available to systemically available steroid. The higher the therapeutic index, the better the risk/benefit ratio.

The *topical effects* depend on the glucocorticoid activity of the molecule and probably also on local pharmacokinetics in the target tissue and cells. The *systemic effects* are related to the glucocorticoid activity of the molecule, the total amount of steroid that gets absorbed (becoming systemically bioavailable) and the rate of clearance of the steroid from the body. The *systemic bioavailability* is the sum of the amount of the drug that becomes systemically available after absorption from the lung, and after gastrointestinal absorption and first-pass metabolism of the swallowed fraction of the dose (Fig. 2). For most of the more recently developed inhaled corticosteroids, the oral bioavailability is low (Table 1); therefore, most of the systemically available

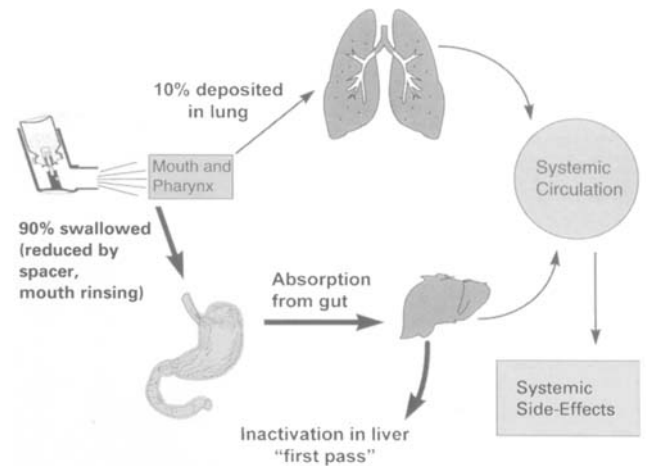


Figure 2. Fate of inhaled steroids. Amount of inhaled corticosteroid reaching systemic circulation is sum of pulmonary and oral bioavailable fractions. Fraction deposited in mouth will be swallowed, and systemic availability will be determined by absorption from gastrointestinal tract and degree of first-pass metabolism. Fraction deposited in intrapulmonary airways is likely to be more or less completely absorbed in active form to systemic circulation, as there is no evidence of any metabolic inactivation of currently available inhaled corticosteroid. Systemic concentration will be reduced by continuous recirculation and inactivation of drug by liver.

steroid comes from the inhaled fraction that enters the systemic circulation after absorption from the lung (1–16).

Both the clinical and the systemic effects of inhaled GCSs may be markedly influenced by the inhaler used by the patient. A higher deposition of drug in the intrapulmonary airways will normally result in a better therapeutic index for those inhaled corticosteroids which are systemically bioavailable by the oral route (Figs. 1 and 2). For inhaled corticosteroids with zero bioavailability after oral dosing, the characteristics of the inhaler device and the patient's inhalation technique determine only the efficacy of the treatment; the therapeutic index is not affected. Moreover, a clinically very effective inhaler with high intrapulmonary deposition of drug will be expected to have a higher systemic effect than a clinically less effective inhaler. These considerations are clinically important, since differences in inhaler characteristics may result in a more than twofold difference in therapeutic index for some inhaled corticosteroids. The influence of various drug-inhaler combinations has been described in detail in recent reviews (17–20). The general conclusions can be summarized as follows.

- 1) Spacer systems are preferred to other inhalers for delivering inhaled steroids with a high systemic availability of drug deposited in the oropharynx (mainly beclomethasone dipropionate (BDP), triamcinolone acetonide, and flunisolide).

Table 1. Relative receptor affinity and basic pharmacokinetic parameters of inhaled steroids. Only budesonide has been studied in children, who have 50% higher clearance than adults

Inhaled steroid	Relative receptor affinity*	T1/2 (h)	Vss (l/kg)	Clearance (l/min)	Water solubility (µg/ml)	Relative topical blanching potency	Oral availability (%)
BDP/BMP	0.5/13	ND	ND	ND	0.1/10	0.6/0.4	(20?)
Budesonide	94	2–3	27	0.9–1.3	14	1	6–13
Flunisolide	19	16	1.8a	10	100	3	21
Fluticasone	220	8–14	121	0.9–1.3	4	1–1.7	<2
Tipredane	270	ND	ND	ND	ND	ND	ND
Triamcinolone acetonide	20	15	13	7	40	4	23

*Dexamethasone was assigned value of 1.
BMP: beclomethasone monopropionate, active metabolite of beclomethasone dipropionate (BDP); ND: not determined.

- 2) A spacer or the dry-powder inhaler Turbuhaler should be preferred for the delivery of budesonide (BUD).
- 3) The low oral bioavailability of fluticasone dipropionate (FP) and mometasone furoate means that the therapeutic index of these drugs does not vary with the delivery system.
- 4) The difference in therapeutic index between the various inhaled corticosteroids and inhaler combinations is clinically most important when high doses of inhaled corticosteroids are used.

Most of the data used to calculate the therapeutic index come from studies in adults. Data available in children suggest that similar considerations would also apply for these age groups. In fact, considerations of the therapeutic index may even be more important in children, whose smaller airway diameter causes a much higher proportion of the inhaled dose to be deposited in the oropharynx, and a lower proportion to be deposited in the intrapulmonary airways than in adults (21).

Although the therapeutic index is the reference standard for characterizing and comparing inhaled corticosteroids, several other outcomes are often used as surrogate markers. The following discussion attempts to summarize the literature on the most commonly used outcomes, pointing out their limitations, the information provided, and their clinical relevance.

Pharmacokinetics

Receptor affinity and retention

Corticosteroids differ in their affinity for the glucocorticoid receptor (Table 1). Although receptor affinity and therapeutic effect appear to show some correlation, there is

no clear-cut relationship, even after correcting for the amounts deposited in the lung. Thus, tipredane has a very high receptor affinity but virtually no therapeutic effect (22). This may be due to the many steps preceding the actual steroid–receptor interaction, which may affect the therapeutic outcome. The steroid must be retained in the target tissue in sufficient concentrations for a sufficient time span if it is to exert any therapeutic effect; it should also readily diffuse through cell membranes with little or no metabolic inactivation, in order to reach the cytosolic glucocorticoid receptor.

Tissue retention of inhaled corticosteroids has not been studied extensively, but the *in vitro* binding of different steroids appears to correlate closely with their lipophilicity (17, 23). *In vivo*, BUD and FP were retained to a similar extent after topical superfusion of rat trachea, and both were retained longer than BDP (24). During washing, the subsequent release of steroid from the tissue was slower for BUD than for any of the other steroids tested. Recently, this retention was reported to be associated with intracellular formation of long-chain fatty-acid conjugates of BUD (25). Intact BUD was released from the conjugates in a rate-limited fashion, and this appeared to prolong the pharmacologic effect of the drug. Neither FP nor hydrocortisone formed corresponding conjugates, and their durations of action were shorter than that of BUD in the tested systems (26, 27). It remains to be studied whether or not this retention mechanism contributes to the duration of therapeutic action and/or the airway selectivity of BUD.

Lipophilicity

Lipophilicity differs markedly among the various inhaled corticosteroids. Theoretically, lipophilicity should be high

to allow a slow dissolution within the lung and free diffusion through cell membranes. However, high water solubility (low lipophilicity) increases the rate of dissolution and concentrations at the receptor site. In addition, high water solubility normally reduces tissue retention and increases elimination. This, in turn, diminishes the risk of systemic effects. Hence, it is difficult to predict what effect a change in lipophilicity will have on the therapeutic index.

Elimination

The elimination half-life, which is a function of both clearance and distribution, differs among the various steroids. Elimination half-life affects the amount of drug present in the body at steady state as well as the rate and extent of accumulation. Accumulation is a function of the frequency of dosing relative to the half-life of the drug; drugs that have a terminal half-life similar to or longer than the dosing interval will accumulate. At present, only FP has been shown to accumulate to an important extent (9, 28). A long elimination half-life also reduces the peak-versus-trough plasma concentration ratio. The clinical importance of differences in half-life is not known. Studies comparing daily and alternate-day dosing of prednisone (29) or once- and twice-daily dosing of BUD (30, 31) have suggested that the effect on the hypothalamus-pituitary-adrenal (HPA) axis is more dependent on persistent plasma levels than on high peak plasma concentrations. The possible influence of once-daily dosing upon the therapeutic index also needs to be studied in more detail.

Pharmacokinetic studies have mainly been conducted in healthy adults or adult patients; only the pharmacokinetics of BUD has been studied in children (21, 32–34). Lung deposition is lower and oropharyngeal deposition higher in children than in adults using the same delivery device (21), and BUD clearance is approximately 50% higher in children than in adults (21, 32). With these exceptions, the pharmacokinetics of BUD in children appears to be similar to that in adults.

Potency

The human skin-blanching (vasoconstrictor) test (35, 36) is believed to reflect potency and the clinical anti-inflammatory effect, and to predict the antiasthmatic effect of inhaled GCSs (37, 38). However, recent comparisons between topically active GCSs have called attention to the need for consistent methodology in such tests, to avoid the confusion of apparently inconsistent results.

Studies using the classic “presence or absence of blanching” method suggested that BDP is approximately half as potent as BUD in the vasoconstrictor assay at both low and high concentrations (39, 40), and more potent than flunisolide. Another study suggested that FP had a more potent skin-blanching effect than BUD (41); this study, however, investigated only the response to low concentrations of both drugs. In contrast, a study which measured the area under the concentration-time curve ($AUC_{1-24\text{ h}}$), in which linear regression lines were plotted over a wide range of concentrations of both GCSs, showed the overall equipotency of BUD and FP (42). It is still not known which method of assessment of skin blanching correlates best with the *in vivo* potency of inhaled GCSs.

The potency of inhaled GCSs has also been assessed by a number of other *ex vivo* methods involving isolated inflammatory or airway tissue cells. This approach has generally demonstrated a greater anti-inflammatory potency for FP than for BUD (43). This type of *in vitro* study, however, does not take into account *in vivo* differences in dissolution and uptake into airway cells and in subsequent tissue binding. Such differences in local pharmacokinetics may also influence the local anti-inflammatory efficacy of inhaled GCSs. Recent findings in comparative studies of the clinical efficacy of BUD and FP in rhinitis emphasize this: two studies found BUD to be clinically more effective than FP on a microgram-for-microgram basis, while a third found the two treatments to be equieffective (44–46). These findings are in contrast to the results of the receptor-affinity studies and some skin-blanching studies, which suggest that FP is as effective as or more effective than BUD.

Due to the uniform distribution of the GCS receptor throughout the body, a high receptor affinity and/or protracted turnover at the receptor site do not, per se, lead to topical selectivity, but only to high local activity. When the GCS is absorbed via the airway or lung, bypassing first-pass metabolism in the gut or liver, a high receptor affinity and/or protracted turnover at the receptor are also likely to be associated with high systemic activity.

Clinical effects

Dose-response trials are the best means of evaluating the clinical effect of inhaled corticosteroids. A number of such studies have assessed the clinical effects of different doses of specific corticosteroids (47); only a few of these have been in children. These studies have provided important information about the use of different corticosteroids or inhalers.

They all report marked and rapid improvements in symptoms and lung function at very low daily doses (around 100 µg) of inhaled steroids in patients with mild, moderate, and severe asthma. Additional improvement in these parameters with increasing doses is rather small, often taking an additional fourfold increase in dose to produce further significant effect. Therefore, low doses are clinically so effective that even very large, well-conducted studies normally fail to show any difference in statistically significant or clinically relevant additional effect on symptoms and lung function between two adjacent doses on the dose-response curve (47).

The dose-response curve for other outcome measures has been less thoroughly studied. It may be less steep in patients with moderate and severe asthma (48), but probably not in patients with mild asthma, who seem to reach the top of the dose-response curve with low daily doses of inhaled steroids.

Another factor which may complicate the interpretation of clinical studies with inhaled GCSs is that differences in the measured response to treatment are influenced by the selected duration of treatment and monitoring. Thus, symptoms of asthma may show a clear response within days, maximal improvement in lung function may not occur for several weeks, and maximal improvement in airway hyperresponsiveness may require several months of inhaled GCS treatment (49, 50). Most dose-response studies of inhaled GCSs have been of rather short duration, so potential differences between the effects of different drugs or doses may not have become apparent on some outcome measures.

Most dose-response studies of individual inhaled GCSs have failed to show statistically significant differences between the clinical effects of adjacent dose steps. Moreover, a fourfold or greater difference in dose is often required to detect a significant (but often small) difference in effect on commonly measured outcome parameters such as symptoms, peak expiratory flow (PEF), and lung function. This makes it very difficult to draw firm conclusions from comparative trials of the clinical effect of different inhaled corticosteroids, particularly if no differences in effect are found between the test drugs.

As discussed earlier, many factors other than dose and drug may influence the clinical effect of inhaled GCSs. These factors should always be considered and presented in comparative trials of inhaled corticosteroids to allow accurate interpretation and comparison of results.

- 1) Trials should be of a randomized, double-blind, and preferably placebo-controlled design. However, the use of different inhaler devices and the need to maintain clinical

control may make such trials almost impossible, especially in patients with severe asthma.

- 2) Precise details of the devices and inhalation technique used to administer the GCS are essential (see above).
- 3) The unit dose delivered by the inhaler may influence the delivered dose. For example, the amount of drug substance delivered to the lungs by five puffs of 50 µg of GCS from a pMDI may be greater than that delivered by one puff of 250 µg from an inhaler of the same type. Again, precise details of the product used should be stated.
- 4) With polycarbonate spacer devices, the time interval between actuation of the pMDI and inhalation should be standardized and specified. The cleaning and washing recommendations given to the trial participants should also be stated, as the state of the spacer device influences its electrostatic charge and thus its delivery characteristics.
- 5) Patients must receive full instruction in the correct use of all inhaler devices included in trials. Without this, results may be confounded by differences in efficacy or ease of use of the inhalers, especially if a familiar inhaler is compared with an unfamiliar inhaler. Precise information about the teaching and monitoring of inhaler use should be provided (51).
- 6) Patient compliance with different forms of inhaled therapy may vary, so some measure of patient compliance should be included and documented.

Each of these factors could influence the measured effect of an inhaled GCS to at least the same extent as doubling or halving the administered dose. Therefore, the value of comparative studies of inhaled GCSs which ignore these factors is doubtful. Furthermore, the difficulty of demonstrating significant differences between individual doses in the dose-response curves for a specific inhaled GCSs is likely to be compounded when different inhaled GCSs are compared, especially if standard outcome parameters such as symptoms, forced expiratory volume in 1 s (FEV₁), or morning PEF are used. This greatly complicates accurate comparison of the effects of different inhaled GCSs, or of the same inhaled GCS administered with different dosing frequency or via different inhaler devices.

The optimal design for a comparative trial of GCSs is not yet established, but true differences between GCSs are most likely to be detected in well-designed trials which control for the factors mentioned above. The various trial designs used and their conclusions have been reviewed elsewhere (47).

Though a substantial number of comparative studies have been performed, it is difficult to draw firm conclusions about the comparative efficacy of different inhaled GCSs. This may be partially explained by differences between the

design of studies, the flat dose-response relationship for inhaled GCSs, and the lack of control of important confounding factors in many studies. BUD administered by Turbuhaler and FP given by Diskhaler appear to be approximately equipotent in efficacy, and these treatment modalities both seem to be more potent (on a nominal dose basis) than BDP administered by pMDI or Rotahaler, or BUD administered by pMDI. However, further well-designed comparisons are required to confirm these suggestions.

Systemic effects

The established inhaled GCSs have an excellent clinical safety profile when given in the doses needed by most patients to achieve symptom control, even with long-term use. However, long-term use of higher doses of inhaled GCS may lead to significant unwanted systemic effects, including adrenal suppression, increased risk of osteoporosis and fractures, and impairment of children's growth. Therefore, it is also important to assess and compare the risk of unwanted systemic effects from various inhaled corticosteroids. This is also required to assess the therapeutic index accurately.

Clinically relevant systemic side-effects should preferably be studied within the context of controlled, long-term clinical trials, which use clinically relevant doses in patients whose disease severities and ages are similar to the groups in which the drugs would normally be prescribed. Such studies require large numbers of patients and are difficult to conduct. As a substitute, the systemic side-effects of the various inhaled corticosteroids are often studied in short-term, standardized, crossover studies on healthy volunteers or patients with mild disease, who will tolerate treatment with placebo for a certain period. The clinical relevance of findings from such studies for patients with moderate and severe asthma is not known. A recent study suggested that significant differences may exist between patients and healthy volunteers (28), the systemic effects being markedly higher in healthy volunteers than in patients.

Long-term studies are in progress, but, in the current absence of results, attempts must be made to assess the risk of long-term adverse effects of inhaled GCSs on the basis of short-term studies. The problem with such attempts is a lack of understanding of the relationship between any changes which may be found in short-term markers and the development of clinically relevant long-term effects.

For better understanding of the various comparisons of different inhaled corticosteroids, some general aspects of the

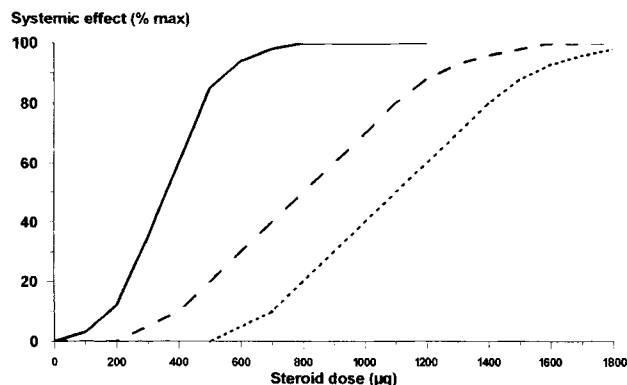


Figure 3.

dose-response relationships of the clinical and systemic effects of inhaled corticosteroids will be briefly discussed.

For a given drug or inhaler, there will always be a dose below which no effect can be detected no matter which investigative method is used (Fig. 3). There will also be a dose range within which an effect is measurable in one or more systems (this dose varies from system to system). Within a certain dose range, there will be a linear (or log linear) relationship between the magnitude of the effect and the dose of drug. At a certain dose, the dose-response curve flattens. Increasing the dose beyond that point is associated with only small changes in the outcome measurement. The most important questions to answer for accurate comparison of the various drugs are as follows (Fig. 3).

- 1) *What is the lowest dose level at which an effect can be detected?* This is important for assessing the sensitivity of comparative trials and defining safe doses.
- 2) *Which dose is required to produce a certain effect (e.g., 50% of maximum)?* This is important for an accurate potency comparison.
- 3) *What is the slope of the dose-response curve?* This is important for an accurate potency comparison and for assessment of the risk of overdosing (therapeutic index): the steeper the slope, the higher the risk.
- 4) *When does the dose-response curve start to become less steep?* This is important for assessing the sensitivity of comparative trials.
- 5) *Are there differences between single and steady-state (repeated) dosing?* This is important for choice of study design and clinical relevance of single-dose studies.

Comparisons of the systemic effects of inhaled GCS therapy have mainly focused on effects upon the HPA axis. Measures of HPA-axis function provide one of the most sensitive and easily measured markers of the systemic effects of inhaled GCS therapy. However, the clinical

significance of small alterations in HPA-axis function measured under controlled, rather artificial laboratory conditions is doubtful. Some reduction in cortisol secretion merely reflects the normal functioning of the HPA-axis feedback control mechanisms in response to exogenous steroid, rather than a clinically significant abnormality, and the total GCS exposure of the body may remain within the physiologic range. Therefore, significant laboratory findings are not necessarily predictive of important clinical effects.

The effects of inhaled GCSs on the HPA axis are often assessed in healthy volunteers, but the clinical relevance of such studies, or studies in patients with mild asthma, to patients with severe asthma requires further study, since some studies suggest that the systemic effects of a given dose of an inhaled corticosteroid may be markedly greater in healthy volunteers than in patients [28].

In contrast to the clinical effect assessments, the systemic effect studies conducted so far allow some conclusions to be drawn [47].

- 1) All the currently available inhaled GCSs have the potential to suppress the HPA axis, and the effect is dose-dependent.
- 2) Overall, the available studies indicate that the systemic potency ratio of BUD to FP depends upon the inhaler devices compared, and on whether the assessment is made on the basis of single or repeated dosing. The systemic potency ratio of FP pMDI to BUD pMDI on a microgram-for-microgram basis has usually been found to be around 3:1; i.e., three times as much BUD is required to produce the same degree of systemic effect as FP. For dry-powder inhalers, this ratio seems to be around 1.5:1 in adults and around 1:1 in children.
- 3) The risk of HPA-axis effects with BDP pMDI also seems to be somewhat higher than that with BUD pMDI, but there is inadequate information to calculate an accurate systemic effect ratio of BDP to BUD or FP.

Summary and discussion

Many different outcomes and models have been used to compare different inhaled corticosteroids. The conclusions from the various models often differ, and there is a great

need for standardization of the various methods. At present, no single model is sufficient to provide the information required to make clinical decisions about the superiority of one inhaled corticosteroid to another.

Differences in pharmacologic properties between drugs are most easily and accurately measured and quantified by measures of systemic effects and pharmacokinetics. However, differences in systemic effects and pharmacokinetic parameters should not be considered in isolation, but should always be related to differences in clinical effects. If an increase in systemic effects is accompanied by a similar increase in clinical effect, the higher systemic effect is not clinically important, since the dose of drug can be reduced to an extent that will balance the potential increase in systemic activity. Therefore, the therapeutic index is the only meaningful way to compare new GCSs, or new GCS/inhaler combinations, with established drugs.

Accurate comparisons of the therapeutic index of different inhaled corticosteroids can only be made in placebo-controlled dose-response studies. Even though a substantial number of such comparative studies have been performed with respect to systemic activity of the various inhaled corticosteroids [17, 47], it is difficult to draw firm conclusions with respect to the therapeutic index, because no direct-dose response comparisons of clinical effects have been made. Moreover, the flat dose-response curve for inhaled corticosteroids makes it very difficult to establish an accurate clinical potency ratio for the various inhaled corticosteroids, since virtually all dose-response trials with the individual drugs have failed to detect significant differences between adjacent doses on the dose-response curve. Finally, since the lung deposition of drug from the various inhalers may differ markedly between children and adults, conclusions from studies in adults should not be applied to children. These studies also have to be conducted in children.

There is a strong need to develop clinical models which can reproducibly distinguish between the effect of two adjacent doses of inhaled GCS on the dose-response curve. Until such models exist, it will be very difficult to compare GCSs or inhalers in an unequivocal and clinically meaningful way unless a more than fourfold difference exists in clinical effect between the two steroids or devices compared.

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