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Measuring efficacy and safety of different inhaled corticosteroid preparations

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Inhaled corticosteroids are the mainstay of treatment for persistent asthma because of their proven efficacy, which is better than any other class of antiasthma therapy. Concerns about unwanted systemic effects with long-term use has, however, limited their use. Efforts have been made to develop inhaled corticosteroids with less systemic activity for a given clinical effect, thereby improving their therapeutic index. Many different study designs and outcome variables have been used to compare different inhaled corticosteroids. Differences in pharmacologic properties between drugs are most easily and accurately measured and quantified by measures of systemic effects. However, these differences should always be related to differences in clinical effects. It is difficult to draw firm conclusions with respect to the therapeutic index of different inhaled corticosteroids because no direct placebo-controlled, dose-response comparisons of clinical effects have been made. Despite this caveat, the available studies suggest that microgram for microgram, when delivered by a pressurized metered-dose inhaler (pMDI), fluticasone propionate (FP) is more effective than beclomethasone dipropionate (BDP), triamcinolone acetonide (TAA), or budesonide; however, the efficacy of budesonide delivered by Turbuhaler is equipotent to that of FP delivered by pMDI or Diskhaler and more effective than that of BDP. When comparative safety is considered, budesonide or TAA delivered by pMDI have less systemic activity than FP delivered by pMDI, whereas BDP and FP delivered by pMDI appear to be equivalent. Also, budesonide delivered by Turbuhaler has less systemic activity than FP delivered by Diskhaler. (*J Allergy Clin Immunol* 1998;102:879-86.)

Abbreviations used

BDP: Beclomethasone dipropionate
FP: Fluticasone propionate
pMDI: Pressurized metered-dose inhaler
TAA: Triamcinolone acetonide

Since their introduction to clinical practice in the early 1970s,¹ inhaled corticosteroids have become the mainstay of treatment for persistent asthma.² This is because of their proven efficacy, which is better than that of any other class of antiasthma therapy. Also, they have a much lower potential for unwanted systemic effects than oral corticosteroids. Nonetheless, the possibility of unwanted systemic effects from long-term use of inhaled corticosteroids is still a concern, especially among pediatricians. Therefore efforts have been made to develop inhaled corticosteroids with even less systemic activity for a given clinical effect.

There are currently 5 inhaled corticosteroids available for the treatment of asthma. These are beclomethasone dipropionate (BDP), triamcinolone acetonide (TAA), flunisolide, budesonide, and fluticasone propionate (FP) (Fig 1), with a sixth, mometasone, soon to be available. Claims are often made that one inhaled corticosteroid has a higher potency and/or a lower potential for systemic unwanted effects than the others, but there is still much debate about the clinical importance of this and about how possible differences should be assessed. This is because both the desired and the unwanted effects of inhaled corticosteroid therapy can be measured in different ways, and the results of different measurements are not always in agreement. This is further complicated by the availability of different inhaler systems as the delivery device for a single corticosteroid or for different corticosteroids. The characteristics of the delivery device may greatly change the risk:benefit ratio of the inhaled corticosteroid. This

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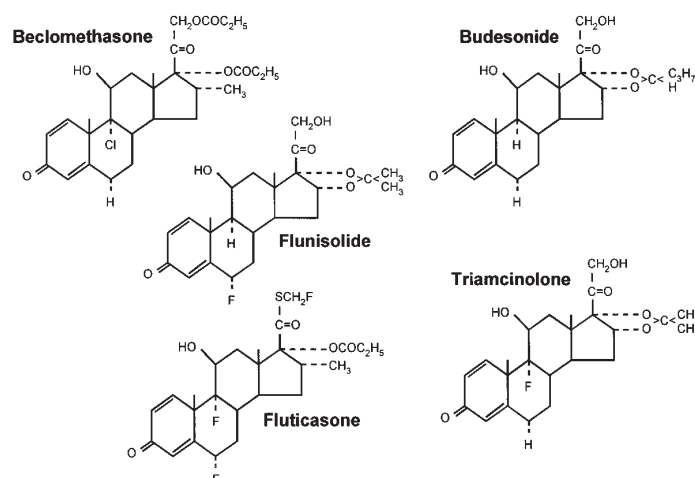


FIG 1. Chemical structures of the inhaled corticosteroids currently available to treat asthma.

makes the whole issue of inhaled steroid therapy complex and confusing for many clinicians. This issue would be greatly clarified if it were possible to calculate risk:benefit ratios for all available combinations of drug and inhaler.

A number of important factors need to be considered when assessing the efficacy and safety of inhaled corticosteroids and comparing the properties of the various drug/inhaler combinations. These factors include issues related to their pharmacokinetics (eg, receptor affinity, plasma half-life, volume of distribution, plasma clearance, and rate of first-pass metabolism) and pharmacodynamics (eg, dose-response characteristics and duration of action), as well as the characteristics of the delivery device (eg, its output, particle size distribution, efficiency of lung delivery, and ease of use). Lack of appreciation of these factors in comparison studies of inhaled corticosteroids can make interpretation of such studies difficult, and interpreting clinical utility on the basis of one of these issues alone can be very misleading. How should inhaled corticosteroids be compared?

The most relevant current parameter for comparing different inhaled corticosteroids, or different formulations of a single inhaled corticosteroid, is the therapeutic index. This is the ratio between the clinical (desired) effects and the systemic (undesired) effects of a drug/inhaler combination. The higher the therapeutic index, the better the risk:benefit ratio. The topical effects depend on the amount of drug delivered to the lungs, on the glucocorticoid activity of the molecule, and probably also on the local pharmacokinetics in the target tissue and cells. The systemic effects are also related to the glucocorticoid activity of the molecule but also 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 total 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.

For the more recently developed inhaled corticosteroids, the oral bioavailability is low (Table I), and therefore most of the systemically available steroid comes from the inhaled fraction that enters the systemic circulation after absorption from the lung.

For inhaled corticosteroids that are systemically bioavailable after the swallowed fraction is absorbed by the gastrointestinal tract, a higher deposition of drug in the intrapulmonary airways will improve the efficacy of the treatment and result in a better therapeutic index. For inhaled corticosteroids with a low bioavailability of the swallowed fraction, the characteristics of the inhaler device and the patient's inhalation technique will not affect the therapeutic index, only the efficacy of the treatment. This is because the only drug available for absorption into the systemic circulation is that fraction that is deposited in the intrapulmonary airways. This means that an inhaler with high intrapulmonary deposition of drug will be expected to have a higher systemic effect than a less effective inhaler. These considerations are clinically important because differences in inhaler characteristics may result in a more than 2-fold difference in therapeutic index for some inhaled corticosteroids.

The majority of the data used to calculate the therapeutic index come from studies in adults. Data available in children suggests 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 deposited in the intrapulmonary airways in comparison with adults.³

The difficulty in measuring the therapeutic index has resulted in several surrogate markers of clinical (wanted) and systemic (unwanted) effects being used to compare inhaled corticosteroids. Here we attempt to briefly summarize the literature on the most commonly used outcomes, pointing out the information they can provide, their limitations, and their clinical relevance.

TABLE I. Relative receptor affinity and basic pharmacokinetic parameters of inhaled steroids

Inhaled steroid	Relative receptor affinity*	Half-life (h)	Volume of distribution (L/kg)	Clearance (L/min)	Water solubility (μg/mL)	Oral availability (%)
BDP/BMP	0.5/13	0.1/6.5	ND	ND	0.1/10	25?
Budesonide	9.4	2-3	2.7-4.3	0.9-1.3	14	6-13
Flunisolide	1.9	1.6	1.8	1.0	100	21
FP	18.0	8-14	3.7-8.9	0.9-1.3	4	<1
Tipredane	27.0	ND	ND	ND	ND	ND
TAA	3.6	2	2.1	7	40	23

Only budesonide has been studied in children, who have a 50% higher clearance than adults.

*Dexamethasone was assessed a value of 1.

BMD, Beclomethasone monopropionate (the active metabolite of BDP); ND, not determined.

PHARMACOKINETICS

Receptor affinity and retention

Corticosteroids differ in their receptor affinity (Table I). There is, however, no absolute relationship between receptor affinity and therapeutic effect, even after correcting for the amounts deposited in the lung. For example, tipredane has a very high receptor affinity but virtually no therapeutic effect.⁴ This may be due to the many steps that precede the steroid-receptor interaction, which may affect the therapeutic outcome. Thus the steroid must be retained in the target tissue in sufficient concentrations for a sufficient time to exert its therapeutic effect. Also, it must readily diffuse over cell membranes with little or no metabolic inactivation to reach the 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 lipophilicity.^{5,6} *In vivo*, after topical superperfusion of rat trachea, budesonide and FP were retained to a similar extent, and both were retained longer than BDP.⁷ During washing, the subsequent release was slower for budesonide than for the other steroids tested.

Recently, this retention was reported to be associated with an intracellular formation of long-chain fatty acid conjugates of budesonide.^{8,9} Intact budesonide was regained 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 duration of action was lower in the tested systems. It remains to be studied whether this retention mechanism contributes to duration of therapeutic action, airway selectivity, or both.

Lipophilicity

Lipophilicity differs markedly between the various inhaled corticosteroids. Theoretically, high lipophilicity will allow a slow dissolution within the lung and free diffusion across cell membranes. However, a high water solubility (low lipophilicity) increases the rate of dissolution and the intracellular receptor site concentration. In addition, a high water solubility normally reduces tissue retention and increases elimination. This in turn diminishes the risk for systemic effects. Hence it is difficult to predict what effect a change in lipophilicity will have on the therapeutic index.

Elimination

Elimination half-life, which is a function of both clearance and distribution, differs between 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 of the same magnitude as the dosing interval or longer will accumulate. At present, only FP has been shown to accumulate to an important extent.^{10,11} 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 versus alternate day dosing of prednisone¹² or once versus twice daily dosing of budesonide^{13,14} have suggested that the detrimental effect on the hypothalamic-pituitary-adrenal (HPA) axis is more dependent on persistent plasma levels than on high peak plasma concentrations. The possible influence of once daily dosing on the therapeutic index also needs to be studied in more detail.

Pharmacokinetic studies have mainly been conducted in healthy adults or adult asthmatic subjects. Only the pharmacokinetics of budesonide have been studied in children.¹⁵ Lung deposition was lower and oropharyngeal deposition higher in children than in adults using the same delivery device.¹⁶ In addition, budesonide clearance was approximately 50% higher in children than in adults. Otherwise, the pharmacokinetics of budesonide in children appeared to be similar to those in adults.

Potency

The human skin blanching (vasoconstrictor) test¹⁷ has been used to reflect the potency and clinical antiinflammatory effect, as well as to predict the antiasthmatic effect,^{18,19} of inhaled corticosteroids. However, recent comparisons between topically active corticosteroids have demonstrated the need for consistent methodology when using this test to avoid the confusion of apparently inconsistent results.

Studies with the classical "presence or absence of blanching" method suggested that BDP is approximately half as potent as budesonide in the vasoconstrictor assay at both low and high concentrations¹⁹ and more potent than flunisolide. One study, which only investigated the

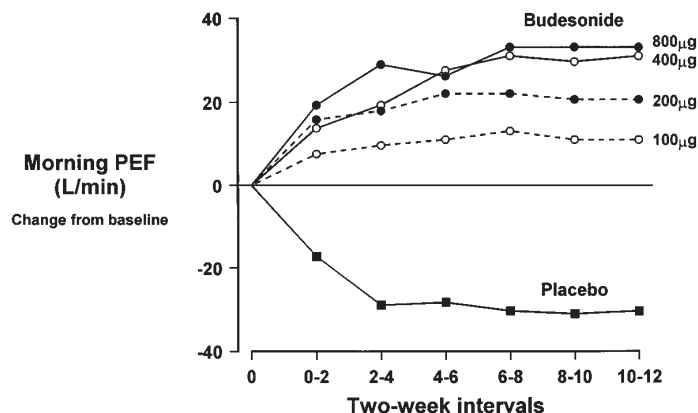


FIG 2. Mean changes from baseline in morning peak expiratory flow (PEF) in patients treated with placebo or various doses of budesonide for 12 weeks of treatment. Significant dose-response is demonstrated; however, the difference between placebo and budesonide 100 µg twice daily is greater than that between 100 and 800 µg twice daily.²⁹

response to low drug concentrations, suggested that FP was more potent than budesonide.²⁰ By contrast, a study with the area under the curve (AUC)₁₋₂₄ hour method, in which linear regression lines were plotted over a wide range of concentrations of both corticosteroids, showed overall equipotency between budesonide and FP.²¹ It is still not known which method of assessment of skin blanching correlates best with the *in vivo* potency of inhaled corticosteroids.

The potency of inhaled corticosteroids 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 budesonide.²² This type of *in vitro* study does not take into account *in vivo* differences in dissolution and uptake into airway cells and subsequent tissue binding. Such differences in local pharmacokinetics may also influence the local anti-inflammatory efficacy of inhaled corticosteroids. Recent findings in comparative studies of the clinical efficacy of budesonide and FP in rhinitis emphasize this.²³⁻²⁵ Two of 3 studies found budesonide to be clinically more effective than FP on a microgram-for-microgram basis. The third found the 2 treatments to be equally effective.

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

CLINICAL EFFECTS

Dose-response studies 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.²⁶⁻²⁹ These studies have provided important information about the use of different corticosteroids or inhalers. They all report marked

improvements in those outcome variables that are most often measured in clinical asthma studies (ie, symptoms and lung function) at low daily doses (100 to 200 µg/day) of inhaled steroids in the type of patients (ie, those with mild or moderate asthma) that are most often studied in these clinical trials. The additional improvement achieved in these parameters by increasing the doses is small, often taking an additional 4-fold increase in dose to produce further statistically significant effects. This means that because low doses are clinically so effective, even very large, well-conducted studies normally fail to show any statistically significant or clinically relevant additional effect on symptoms and lung function between 2 adjacent doses on the dose-response curve (Fig 2).^{26,28,29} This means that it is very difficult to draw conclusions from comparative trials of the clinical effect of halving or doubling doses of different inhaled corticosteroids when no significant differences are found in effect between the test drugs.

Another factor that may complicate the interpretation of clinical studies with inhaled corticosteroids is that differences in the measured response to treatment are influenced by the duration of treatment and monitoring. This is because symptoms of asthma may show a clear response within days, maximal improvement in lung function may not occur for several weeks,³⁰ and maximal improvement in airway hyperresponsiveness take months to years of treatment with inhaled corticosteroids.³¹ Most dose-response studies of inhaled corticosteroids have been of short duration, and therefore potential differences between the effects of different drugs or doses may not have become apparent for some outcome variables.

It is clear that many factors, other than dose and drug, may influence the clinical effect of inhaled corticosteroids. These factors should always be considered and presented in papers describing comparative trials of inhaled corticosteroids to allow accurate interpretation and comparison of results. Some of the more important of these factors are as follows.

- Trials should be of a randomized, double-blind, and preferably placebo-controlled design. However, the

TABLE II. Studies of comparative efficacy of inhaled corticosteroids when a dose efficacy could be estimated

Drugs compared	Patients	Doses (μ g)	Duration	Outcome variable	Efficacy ratio	Reference
BDP pMDI vs BUD pMDI	Adults	400, 1000 vs 400, 800	22 wks	PEF AM	BDP:BUD 1:1	47
BDP pMDI vs FP pMDI	Adults	400 vs 100, 200, 400, 800	4 wks	PEF	FP:BDP 2:1	26
BDP pMDI vs BUD Turbuhaler	Adults	Dose adjustment	12 wks	Symptoms, PEF	BUD:BDP 1.7:1	48
BUD pMDI vs FP pMDI	Adults	1600 vs 1000, 2000	6 wks	PEF	FP:BUD 1.8:1	49
BUD Turbuhaler vs FP Diskhaler	Adults	200, 400 vs 200, 400	6 wks	Symptoms, PEF, FEV ₁	FP:BUD 1:1	50
BUD Turbuhaler vs FP Diskhaler	Children	400, 800 + dose adjustment vs 400, 800	Variable	Symptoms, PEF	FP:BUD 1:1	51
TTA pMDI vs FP Diskhaler	Adults	800 vs 500	24 wks	PEF	FP:TTA >1.6:1	32

BUD, Budesonide; PEF, peak expiratory flow.

use of different inhaler devices and the need to maintain asthma control may make such trials almost impossible, especially in patients with severe asthma.

- Precise details of the devices and inhalation technique used to administer the corticosteroid are essential.
- The unit dose delivered by the inhaler may influence the delivered dose. The amount of drug substance delivered to the lungs by 5 puffs of 50 μ g of a corticosteroid from a pMDI may, for example, be greater than that delivered by 1 puff of 250 μ g from an inhaler of the same type.
- The time interval between actuation of the pMDI and inhalation should be standardized and specified when polycarbonate spacer devices are used as part of the delivery system. The cleaning and washing recommendations given to the trial participants should also be described because the condition of the spacer device influences its electrostatic charge and thus its delivery characteristics.
- 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.
- Patient compliance with different forms of inhaled therapy may vary, and therefore some measure of patient compliance should be included and documented.

Each of these factors could influence the measured effect of an inhaled corticosteroid by at least the same extent as doubling or halving the administered dose. The value of comparative studies of inhaled corticosteroids that ignore these factors is therefore doubtful. The optimal design of a comparative trial of corticosteroids is not yet established, but true differences between corticosteroids are most likely to be detected in well-designed trials that control for these factors.

The various trial designs used and their conclusions have been recently reviewed elsewhere.² Although a substantial number of comparative studies have been performed, it has

been difficult to draw firm conclusions about the comparative efficacy of different inhaled corticosteroids for all of the reasons discussed above. However, these studies have suggested that budesonide administered by Turbuhaler and FP administered by Diskhaler are 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 budesonide administered by pMDI (Table II). Moreover, fluticasone administered by Diskhaler seems clinically more potent on a microgram-for-microgram basis than TAA administered by pMDI.³² Further well-designed comparisons are, however, required to confirm these suggestions.

UNWANTED SYSTEMIC EFFECTS

The established inhaled corticosteroids have an excellent clinical safety profile when used in doses needed by most patients to achieve symptom control, even with long-term use. However, concern exists about the long-term use of higher doses of inhaled corticosteroids leading to significant unwanted systemic effects, including adrenal suppression,^{33,34} bone demineralization,³² and, in children, impairment of growth.^{36,37} Therefore it is important also to assess and compare the risk of systemic unwanted effects from various inhaled corticosteroids. This information is also required to accurately assess the therapeutic index.

Clinically relevant unwanted systemic effects should ideally 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 effects of the various inhaled corticosteroids are often studied in short-term, cross-over studies on healthy volunteers or patients with mild disease who will tolerate treatment with placebo for a certain period. A recent study suggested that unwanted systemic effects are higher in

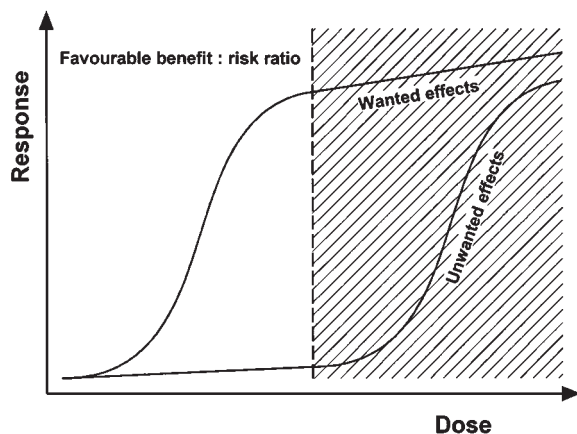


FIG 3. Schematic dose-response curves for the wanted and unwanted effects of inhaled corticosteroids. The range in which the risk:benefit ratio is favorable is that at which the wanted effects in the lungs increase steeply with dose while the unwanted systemic effects increase gradually. At higher doses, the increase in risk greatly outweighs the slight remaining increase in benefit. This relationship appears to vary for different inhaled corticosteroids. Reprinted with permission from *Allergy*. 1997;52:1-34.

healthy volunteers than asthmatic subjects.¹¹ Therefore the clinical relevance of findings from such studies for patients with moderate and severe asthma is not known.

To better understand the comparisons of the systemic unwanted effects of different inhaled corticosteroids, some general aspects of the dose-response relationships of inhaled corticosteroids need to be considered (Fig 3). 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. There will also be a dose range within which an effect is measurable for one or more outcomes. 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 out. Increasing the dose beyond that point is associated with only small changes in the outcome measurement. This means that the most important information that needs to be obtained to accurately compare the various drugs is as follows:

- the lowest dose level at which an effect can be detected, which is important for defining safe doses;
- the dose required to produce a certain effect (ie, 50% of maximum), which is important for an accurate potency comparison;
- the slope of the dose-response curve, which is important for an accurate potency comparison and for assessment of the risk of overdosing (the steeper the slope, the higher the risk);
- the dose at which the dose-response curve starts to flatten out, which is important to assess the appropriateness of dosing in comparative trials;
- differences between single and steady state (repeated) dosing, which is important for choice of study design and to understand clinical relevance of single-dose studies.

Comparisons of the systemic effects of inhaled corticosteroids have mainly focused on their effects on the

HPA axis. Measures of HPA-axis function provides the most sensitive and easily measured markers of systemic effects of inhaled corticosteroid therapy. The clinical significance of small alterations in HPA-axis function measured under controlled, artificial laboratory conditions is doubtful, however. Some reduction in cortisol secretion merely reflects the normal functioning (feedback) of the HPA-axis control mechanisms in response to exogenous steroid rather than a clinically significant abnormality, and the total corticosteroid exposure of the body may remain within the physiologic range. Significant laboratory findings are therefore not necessarily predictive of important clinical effects.

Despite these limitations and in contrast to the clinical effect assessments, the systemic effect studies conducted so far do allow some conclusions.

- All the currently available inhaled corticosteroids can produce suppressive effects on the HPA axis, and the effect is dose-dependent.³⁸⁻⁴²
- Overall, the systemic potency ratio of budesonide to FP depends on the inhaler devices compared and on whether the assessment is after single or repeated dosing. The systemic potency ratio between FP and budesonide administered by pMDI on a microgram-for-microgram basis has usually been around 3:1 (ie, three times as much budesonide is required to produce the same degree of systemic effect as FP) (Table III).⁴²⁻⁴⁴ For the dry powder inhalers, this ratio seems to be around 1.5:1 in adults⁴⁰ and around 1:1 in children.⁴⁵
- The risk of HPA-axis effects with BDP administered by pMDI is somewhat higher than that with budesonide administered by pMDI,¹⁹ but there is inadequate information to calculate an accurate systemic effect ratio for BDP versus budesonide or FP.
- Higher doses of FP demonstrated a 2-fold greater effect on the HPA axis when compared with higher doses of TAA in adult asthmatic subjects (Table III).⁴⁶

CONCLUSIONS

Many different study designs and outcome variables have been used to compare different inhaled corticosteroids. The conclusions from studies comparing the same inhaled corticosteroids often differ, and there is a great need for standardization of the study designs and methods used. At present, no single study design is sufficient to provide the information required to make clinical decisions about superiority of one inhaled corticosteroid over another.

Differences in pharmacologic properties between drugs are most easily and accurately measured and quantified by measures of systemic effects and pharmacokinetic parameters. However, these differences 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 because 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 meaning-

TABLE III. Studies of comparative safety of inhaled corticosteroids when a systemic ratio of HPA-axis effects could be estimated

Drugs compared	Patients	Doses (μg)	Duration	Outcome variable	Systemic ratio	Reference
BDP pMDI vs BUD pMDI	Normal adults	200, 800, 3200 vs 200, 800, 3200	Single dose	4-hour AUC plasma cortisol	BDP:BUD 2:1	19
BDP pMDI vs BUD pMDI	Asthmatic children	800-1200 vs 800-1200	6 wks	24-hour urine cortisol	BDP:BUD 1.5:1	38
BDP pMDI vs BUD pMDI	Asthmatic children	400 vs 400	4 wks	Nocturnal AUC serum cortisol, 24-hour urine cortisol	BDP:BUD 1:1	52
BDP pMDI vs FP pMDI	Asthmatic adults	1500 vs 1500	1 year	Urine-free cortisol	BDP:FP 1:1	53
BUD pMDI vs FP pMDI	Normal adults	400, 800, 2000 vs 400, 750, 2000	4 days	24-hour AUC plasma cortisol	FP:BUD 3.7:1	42
BUD pMDI vs FP pMDI	Asthmatic adults 500, 1000, 1500, 2000	400, 1000, 1600, 2000 vs	Single dose	Overnight urine cortisol	FP:BUD 2.9:1	43
BUD pMDI vs FP pMDI	Asthmatic children	400, 800, 1250 vs 400, 800, 1250	Single dose	Overnight urine cortisol	FP:BUD 2.9:1	44
BUD Turbuhaler vs FP Diskhaler	Normal adults 200, 400, 1000, 2000	200, 400, 800, 1600 vs	1 wk	24-hour AUC plasma cortisol	FP:BUD 1.7:1	54
TAA pMDI vs FP pMDI	Adult asthmatic subjects	400, 800, 1600 vs 330, 770, 1540	3 days	Overnight urinary cortisol	FP:TAA 2:1	46

BUD, Budesonide; AUC, area under the curve.

ful parameter to compare when new corticosteroids or new corticosteroid/inhaler combinations are compared with the established drugs.

Accurate comparisons of the therapeutic index of different inhaled corticosteroids can only be made in placebo-controlled, dose-response studies. Even if a substantial number of such comparative studies have been performed with respect to systemic activity of the various inhaled corticosteroids,² 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 higher doses of inhaled corticosteroids makes it very difficult to establish an accurate clinical potency ratio between the various inhaled corticosteroids because virtually all dose-response studies with the individual drugs have failed to detect significant differences between adjacent doses on their own dose-response curves. There is a need to develop clinical models that can reproducibly differentiate between the effect of 2 adjacent doses of inhaled corticosteroids on the dose-response curve. Until such models exist it will be very difficult to compare corticosteroids or inhalers in an unequivocal and clinically meaningful way unless a more than 4-fold difference exists in clinical effect between the 2 steroids or devices compared.

Despite all of these caveats, the available studies suggest that microgram for microgram, when delivered by pMDI, FP is more effective than BDP, TAA, or budesonide; however, the efficacy of budesonide delivered by Turbuhaler is equipotent to that of FP delivered by pMDI

or Diskhaler and more effective than BDP. When comparative safety is considered, budesonide or TAA delivered by pMDI have less systemic activity than FP delivered by pMDI, whereas BDP and FP delivered by pMDI appear to be equivalent. Also, budesonide delivered by Turbuhaler has less systemic activity than FP delivered by Diskhaler.

Finally, because 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.

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