Journal of Clinical Pharmacy and Therapeutics (2009) **34**, 1–12 doi:10.1111/j.1365-2710.2008.00970.x

REVIEW ARTICLE

Inhaled corticosteroids for asthma: are they all the same?

A. P. Baptist* MD MPH and R. C. Reddy† MD

*Divisions of *Allergy and Clinical Immunology and †Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA*

SUMMARY

Objectives: **To assess similarities and differences among currently available inhaled corticosteroids (ICS) for treatment of asthma, with special emphasis on factors that may affect the relative safety of these medications.**

Methods: **PubMed was searched for relevant reviews and original articles. Information from these studies was synthesized and critically assessed.**

Results: **Differences in corticosteroid formulations and delivery systems can create variations in therapeutic efficacy. Chemical properties of the various corticosteroids may also affect their relative safety. Ciclesonide and beclomethasone dipropionate are administered as prodrugs activated by enzymes present in the lungs but not the oropharynx. Corticosteroid-specific adverse effects in the oropharynx are thus avoided, although formulation-specific effects may remain. Other adverse effects require systemic availability, either via the gastrointestinal tract or the lung. Once they enter the systemic circulation, all ICS are rapidly metabolized by the liver. Oral bioavailability of ICS such as fluticasone, ciclesonide and mometasone is minimal, as a result of their essentially complete first-pass metabolism in the liver. Ciclesonide also undergoes extrahepatic metabolism that eliminates it even more rapidly. Additionally, ciclesonide and mometasone exhibit very high levels of binding to serum proteins that reduces their ability to stimulate glucocorticoid receptors outside the lung.**

Conclusions: **Despite acting by similar mechanisms, currently available ICS and their delivery systems differ in ways that can potentially affect both safety and therapeutic effectiveness for individual patients.**

***Keywords*: candidiasis, ciclesonide, dysphonia, fluticasone, glucocorticoid, inhalers**

Received 06 March 2008, Accepted 24 July 2008

Correspondence: Raju C. Reddy, MD, Division of Pulmonary and Critical Care Medicine, University of Michigan Medical Center, 109 Zina Pitcher Place, 4062 BSRB Ann Arbor, MI 48109-2200, USA. Tel.: +1 734 615 2871; fax: +1 734 615 2111; e-mail: rajuc@umich.edu

INTRODUCTION

Inhaled corticosteroid therapy (ICS) revolutionized the management of patients with asthma (1). For the first time, it was possible to provide long-term control of symptoms without the serious systemic side-effects of oral corticosteroids. This was not, however, the first use of inhalers in asthma patients. Metered-dose inhalers had been introduced in the 1950s for delivery of short-acting β-agonist bronchodilators. This was followed approximately a decade later by introduction of dry-powder inhalers for delivery of sodium cromoglycate. The first ICS was beclomethasone, introduced in the early 1970s. Clinical trials quickly demonstrated that patients previously maintained on low-dose oral corticosteroids could be partially or completely transferred to inhaled beclomethasone dipropionate with greater safety and little loss of efficacy (2–4).

Today, ICS are the recommended first-line therapy for persistent asthma of all severities and patients of all ages (5) and are the most effective asthma medications currently available. Limitations and drawbacks remain, however. Whether corticosteroids can inhibit the airway remodelling characteristic of chronic asthma remains controversial. Furthermore, an estimated 5–10% of all asthma patients do not respond adequately to even oral steroids (6–8). Additionally, although side-effects of ICS are less frequent and less severe than those of oral steroids, safety concerns remain.

POTENTIAL ADVERSE EFFECTS

Effects in the oropharynx

Although use of inhaled as compared with oral steroids dramatically reduces the incidence and severity of systemic adverse effects, they raise the possibility of local adverse effects specifically in the oropharyngeal cavity. A significant fraction of the delivered dose, perhaps as much as 90% (9), may be deposited in the mouth and pharynx without ever reaching the lungs.

The mechanisms underlying local adverse effects of these oropharyngeally deposited corticosteroids have not been extensively investigated, but appear to include both immunologic and non-immunologic actions. It is presumably suppression of local immunity that leads to the increased risk of oral candidiasis seen with use of ICS. The extent of the risk is unclear, however, perhaps in part because *Candida* colonization is often unassociated with clinical symptoms (10), so studies reporting colonization and those reporting clinical candidiasis are not truly comparable. One study covering almost 26 000 patients age 65 and older who were using ICS found a 3-year oral candidiasis incidence of 7% (11), but whether this frequency would be observed in patients of other ages remains uncertain. Fortunately, the condition is usually easy to treat.

Dysphonia accompanying ICS use is common. The true frequency remains unclear, however, with reported incidences ranging from 5 to 50% (12). The variations in reported incidence may reflect both varying methods of ascertainment, often patient questionnaires or incidental findings, and varying definitions that may or may not differentiate dysphonia from hoarseness of other aetiologies. Steroid-associated dysphonia has sometimes been attributed to myopathy affecting the muscles that control the vocal cords, but laryngoscopic findings have been inconsistent (13). One study found that switching from a metered dose inhaler to a dry powder inhaler significantly reduced the frequency of dysphonia, possibly because of differences in position of the vocal cords during use of the two devices (14).

Persistent cough and bronchospasm are relatively uncommon side-effects of ICS use (13). However, reflex cough during inhalation is quite common. One study observed reflex cough in 34% of a mixed-age population using either beclomethasone dipropionate or budesonide (15). Both this study and another (16) found that use of a large-volume spacer did not reduce the frequency of cough. They likewise found no effect of differences in the medications tested. Lack of any difference among ICS in the frequency of reflex cough could point toward this being due to the propellant or to irritant properties of other components of the formulation.

In principle, steroid effects in the oropharyngeal cavity can be avoided by administering the agent as a prodrug that must be activated with an enzyme present in the lung but not in the upper respiratory tract. Ciclesonide is one such agent and its prodrug status has often been cited as an advantage. A pooled analysis found a lower incidence of oropharyngeal adverse effects compared with fluticasone, budesonide and beclomethasone dipropionate as a group (13). It is difficult to tell from the available data whether differences between ciclesonide and beclomethasone dipropionate, which is also administered as a prodrug, were observed in this analysis. However, as other studies have found little difference between beclomethasone dipropionate and budesonide, the prodrug concept remains open to question (13).

Suppression of the hypothalmic–pituitary–adrenal (HPA) axis

Glucocorticoid secretion is governed by a negative feedback loop in which activation of hypothalamic glucocorticoid receptors results in reduced secretion of corticotrophin-releasing hormone. This leads to a decrease in release of adrenocorticotrophic hormone (ACTH) by the pituitary and consequently of cortisol and other glucocorticoids by the adrenal gland. As exogenous glucocorticoids activate the hypothalamic glucocorticoid receptor, they suppress production of endogenous glucocorticoids. Long-term, high-level suppression can render endogenous production slow to recover, so that sudden withdrawal of the exogenous agent can result in acute adrenal insufficiency and adrenal crisis (17). There has also been concern about possible adverse effects of lesser degrees of HPA axis suppression, although this is controversial.

Even one-time administration of ICS has been shown to produce measurable HPA axis suppression. For example, a 500 μg dose of

fluticasone administered via a dry-powder inhaler produced a 29% reduction in nocturnal cortisol secretion compared with the preceding night's values (18). Another study found that fluticasone doses of 250, 500 and 1000 μg reduced plasma cortisol area under the concentration–time curve (AUC) for the first 20 h after dosing by 8%, 19% and 28%, respectively, while a 800 μg dose of budesonide reduced values by 16% (19). These modest single-dose reductions are unlikely to be clinically significant. However, a cross-sectional study has found clearly abnormal (<5 μg/dL) morning cortisol levels in 10 of 28 patients receiving >660 μg of fluticasone for a year or more (20). All of these patients also exhibited a low response to ACTH stimulation. Furthermore, a survey in the UK found that adrenal crisis had been identified in 33 ICS users among the patients of 709 responding physicians (21). Most of these cases were children receiving fluticasone and clinical practice recommendations have since been changed to eliminate the doses at which adrenal crisis was reported.

Other safety concerns

Skin thinning and ecchymoses. Use of ICS is associated with reduced synthesis of skin collagen (22), which at higher doses leads to skin thinning and ecchymoses (23) as well as to slow healing of skin cuts and sores (24). Frequent bruising has been documented in a number of large studies (24–27), presumably reflecting capillary fragility as a result of impaired collagen synthesis.

Decreased bone mineral density. Effects of ICS on bone mineral density are controversial. Confounding factors include previous use of oral corticosteroids and respiratory-related lifestyle changes, such as limited exercise, that may themselves affect bone mineral density. However, even studies designed to limit or avoid effects of oral corticosteroid use may give conflicting results (28–31), as do studies with biochemical markers of bone formation and degradation (32–34). One particularly well-designed study enrolled only patients aged 20–40 with little or no previous oral corticosteroid use. With major confounding factors controlled, a negative relationship between bone mineral density and cumulative lifetime dose of ICS was observed (35). This is in accord with the consensus of reviewers that long-term, high-dose use of ICS may have significant effects on bone mineral density (36–38), although a Cochrane review disagrees (39). The Cochrane meta-analysis of seven studies meeting inclusion criteria concluded that there was no evidence of increased loss of bone mineral density or of fracture risk and that increases in osteocalcin levels (a measure of bone mineral degradation) were seen only at doses above those usually recommended.

Cataracts and glaucoma. Evidence for an association between ICS use and development of posterior subcapsular cataracts is likewise not completely consistent. One small study found that cataract incidence was associated only with prednisone use (40). Two larger studies, however, have found an association with dose and duration of ICS use (41, 42). A recent meta-analysis has reached the same conclusion, finding that ICS increased cataract risk significantly (43).

One large case–control study found an increased risk of glaucoma or ocular hypertension with high doses of ICS but not with ICS use in general (44). Initiation of ICS use likewise showed no effect on glaucoma incidence in a smaller prospective study (45). Glaucoma thus does not seem to be a general concern in patients receiving ICS, although measurement of intraocular pressure may be appropriate in select patients receiving high doses.

Although safety concerns remain with ICS, these do not offset the established beneficial profile of these drugs. Most strikingly, one study has found that prescribing an ICS to elderly patients being discharged following an asthma-related hospitalization resulted, after adjustment for confounders, in a 29% relative reduction in the risk of rehospitalization and a 39% reduction in the risk of death during the following year (46). Nevertheless, the National Heart, Lung, and Blood Institute's Expert Panel recommends use of the lowest possible ICS dose that maintains asthma control, with consideration being given to adding a long-acting β-agonist to low- or medium-dose ICS therapy in preference to further escalation of the ICS dose (5). The panel also recommends calcium and vitamin D supplements, and possibly bisphosphonates where indicated.

PHARMACOKINETICS AND PHARMACODYNAMICS OF ICS

Oral and pulmonary bioavailability

Inhaler-delivered corticosteroids become systemically available by one of two routes. A large fraction is deposited in the oropharyngeal cavity and is then swallowed. Varying amounts will be absorbed into the enterohepatic circulation and subjected to first-pass metabolism in the liver. Oral bioavailability (Table 1), which is defined as the fraction of an oral dose that reaches the systemic circulation, reflects both the fraction absorbed and the fraction escaping first-pass metabolism. As an example, the oral bioavailability of budesonide is approximately 11% (47). The oral bioavailability of beclomethasone, however, is approximately 41%, with 26% of an inhaled dose becoming systemically available via the gastrointestinal tract (48). By contrast, the oral bioavailability of fluticasone and ciclesonide is ≤1%, representing essentially complete first-pass metabolism (49–51).

Essentially all drug that reaches the lungs and is not removed by mucociliary clearance will eventually enter the systemic circulation. This means that pulmonary bioavailability is determined by inhaler design and the patient's technique of usage, along with size and physical properties of the particle, but not by the chemical identity of the drug. As typical examples, the pulmonary deposition, and hence bioavailability of ciclesonide using a hydrofluoroalkane inhaler is 52% while that of fluticasone is only 16% using the same inhalation device (52). The difference probably reflects a difference in formulation (solution vs. suspension). Particle size and composition also affect how deeply the particle penetrates into the lung. Distal, even deposition is therapeutically desirable but does not ultimately influence systemic availability.

The absolute bioavailability of any ICS, defined as oral plus pulmonary bioavailability, is always less than 100%. Notably, the absolute bioavailability of fluticasone is only about 16% (50). This reflects a combination of incomplete absorption from the gut and first-pass metabolism.

Table 1. Oral bioavailability of inhaled corticosteroids

Steroid	Oral bioavailability
Beclomethasone dipropionate	(48)
As unchanged compound	<1%
As beclomethasone 17-monopropionate	41%
Budesonide	11–13% (47, 73)
Ciclesonide	<1% (49)
Flunisolide	7% (77)
Fluticasone	≤1% (50, 78)
Mometasone	No data available[a]
Triamcinolone	23% (79)

[a]Total systemic bioavailability has been reported as <1% after a single inhaler-delivered dose and as 11% after multiple doses (80).

Pulmonary residence time

As ICS act therapeutically in the lung, it would seem desirable for a drug to reside longer in the lung before entering the systemic circulation. Whether increased pulmonary residence time, defined as the mean time between inhalation and systemic absorption, actually increases the receptor's total exposure to active drug depends on the mechanisms involved.

One factor affecting pulmonary residence time is the rate at which inhaled particles dissolve. This calls for a careful balance in drug design. A highly soluble drug may dissolve quickly, giving a rapid peak in drug concentration that then falls rapidly as the drug enters the bloodstream. If the drug dissolves too slowly, however, the particles may be swept out of the lung by mucociliary clearance. The rate of dissolution is affected by particle size, the physical characteristics of the inhaled particle and the chemical characteristics of the drug. The possibility that dissolution rate may be modified by such formulations as coated particles and microspheres is currently under investigation.

The other way in which pulmonary residence time can be increased is by esterification of the drug to a fatty acid. These esters are very highly lipophilic and will typically be sequestered in the cell membranes until the ester bond is hydrolysed in the course of normal cell metabolism. However, these membrane-bound esters are not available to activate pulmonary glucocorticoid receptors. Thus, the net effect is to maintain a pulmonary reserve of inactive drug. This ensures relatively steady levels of active drug without increasing total receptor exposure. Formation of

these fatty acid esters requires that the drug have an unhindered hydroxyl at position 21. Such a hydroxyl is present in budesonide (53), triamcinolone (54) and the active metabolite of ciclesonide, desisobutyryl-ciclesonide (55). Esters of desisobutyryl-ciclesonide have been shown to persist in the lung for more than 24 h (55).

Lung-specific activation

Beclomethasone dipropionate and ciclesonide are administered as prodrugs that are activated in the lung by esterase activity. Beclomethasone is administered as the 17,21-dipropionate. Since a free hydroxyl group at the 21 position is required for activity, the prodrug is inactive until esterases in the lung convert it to the active 17-monopropionate and later to the less-active parent compound (48). Ciclesonide is a 21-isobutyryl ester that is hydrolysed by the same enzymes to the active desisobutyryl-ciclesonide (56).

The relevant esterases are not present in the oropharynx, so administration as a prodrug is expected to improve oropharyngeal safety. These enzymes are present elsewhere in the body, however, so any drug that escaped activation in the lung will still be activated once it enters the systemic circulation and can potentially contribute to systemic adverse effects. The simultaneous presence of active and inactive forms complicates study of the pharmacokinetics, though.

Lipophilicity

A highly lipophilic drug passes readily through the cell membrane and thus reaches the glucocorticoid receptor. This is equally true in the lung and in extra-pulmonary tissues. Thus, both benefit and risk are increased without any necessary alteration in their ratio. An additional effect, however, is that a larger fraction of a highly lipophilic drug will leave the bloodstream and be temporarily sequestered in body tissues. In single-dose studies, this will decrease the amount present in the bloodstream. With chronic dosing, however, the drug will accumulate in the tissues and an equilibrium will be reached. Thus, once again, the effect will be to dampen concentration fluctuations without affecting the amount available on average to the receptor.

The apparent volume of distribution is the volume that the total amount of drug in the body would occupy if it were uniformly distributed at the concentration in the blood. It is thus a measure of the extent to which the drug leaves the bloodstream and is sequestered in the tissues. Exchange between blood and tissue, however, is an equilibrium process that reflects the amount of unbound drug in each compartment as well as the ease with which drug passes from one compartment to another. A high level of binding to plasma proteins tends to retain drug in the blood whereas high liopophilicity is among the factors that contribute to tissue entry and to binding and retention in the tissues. Reflecting the balance of these two factors as well as others, measured distribution volumes range from approximately 180 L for budesonide to almost 900 L for the active metabolite of ciclesonide (52). Although apparent volume of distribution influences drug half-life, the important factors determining steady-state safety and efficacy are lipophilicity and protein binding individually rather than their combined effects on volume of distribution.

Systemic clearance

Once a drug has entered the bloodstream, the rate at which it is removed from the body becomes important. Corticosteroids are metabolized primarily by the liver and the clearance is typically similar to or somewhat lower than the hepatic blood flow rate (52). However, clearance of the active metabolite of ciclesonide considerably exceeds hepatic blood flow, indicating involvement of extrahepatic sites of inactivation (57). As rapid clearance decreases the AUC, such extrahepatic inactivation is desirable and is likely to be a common feature in ICS introduced in the future.

An additional consideration is the extent to which corticosteroids in the bloodstream are bound to plasma proteins, predominantly albumin (Table 2). Protein-bound corticosteroids do not activate the glucocorticoid receptor. One might in principle expect them to also be partially protected from inactivation, but first-pass hepatic clearance of ICS is so efficient that the effect is negligible in practice. Thus, protein binding that renders the drug unavailable during the period between absorption from the lung and the time it reaches

Table 2. Protein binding of inhaled corticosteroids (Adapted from (52) except as noted)

Steroid	Protein binding (%)
Beclomethasone	87
Budesonide	88
Ciclesonide	99
Flunisolide	80
Fluticasone	90
Mometasone	98 (81)
Triamcinolone	71

the liver is an almost unqualified advantage. Reported protein binding for currently available ICS ranges from 71% for triamcinolone to 99% for ciclesonide and its active metabolite (52). There has been a general trend toward increased protein binding by newer ICS, and it is likely that 97–99% binding will remain standard for any that may be introduced in the future.

Potency

Potency (Table 3) is affinity for the receptor, that is, the fraction of receptor bound and activated at a given drug concentration. As the same receptor is responsible for both therapeutic and adverse effects, high potency would not in itself alter the risk/benefit ratio. However, whereas the therapeutic effect of most ICS appears to plateau at doses only modestly above those currently recommended (7) – for example, evidence indicates that there is no therapeutic advantage to increasing the budesonide dosage above 1600 μg/day (58) – this appears to be less true for the newer, more potent corticosteroids fluticasone (59) and ciclesonide (60). The same may be true for mometasone (61), where one study in patients with severe, persistent asthma found that doses ranging up to 1600 μg/day (four times the usual dose) allowed 76% of those patients to completely eliminate usage of oral prednisone (62). Such dose escalation becomes particularly attractive when high potency is combined with low oral bioavailability.

Table 3. Rank order of inhaled corticosteroid potency (highest to lowest)

Mometasone (82)
Fluticasone (82–84) ≈ Ciclesonide (83)
Budesonide (84) ≈ Triamcinolone (84)
Flunisolide (84)

METHODS OF DELIVERY TO THE LUNG

Since the therapeutic target of ICS is the lung, a method for delivery to that site is required. The ideal goal would be to deliver drug specifically to the lung and nowhere else, but unfortunately none of the current methods approach that goal. Nevertheless, there are significant differences among the currently available delivery methods.

There are currently three methods by which corticosteroids can be delivered to the lung: metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers. MDIs have the drug either dissolved or suspended in a liquefied, pressurized propellant. Pressing the actuator button briefly releases the pressure, converting a measured amount of propellant into an aerosol delivered from the orifice. Older MDIs used chlorofluorocarbons (CFCs) as the propellant, but following adoption of the Montreal Protocol on Substances That Deplete the Ozone Layer those were gradually phased out in favour of the hydrofluoroalkanes (HFAs) used today. MDIs require the patient to inspire as the button is pressed, a technique that many find difficult to master. Indeed, fully three-quarters of patients (63) do not use the correct technique while more than 40% of nurses and faculty at an academic medical center perform at least four of the seven steps incorrectly (64). This is one factor that has led to adoption of large-volume spacers or holding chambers for use with MDIs, since these devices retain the drug within the chamber until the patient breaths in. They also facilitate anatomically correct placement of the device outlet and reduce the shock of cold propellant hitting the back of the throat that sometimes causes patients to halt inspiration. These spacers significantly increase the overall bulk of the device, however, and attention to technique is still required.

With DPIs, it is the patient's own inspiration that provides the energy for drug delivery. That breath draws air through the drug, formulated as a dry powder. The drug is then entrained in the inspired

air, with screens or spinning surfaces used to break up the aggregates that micronized particles would otherwise form. DPIs do not require hand-breath coordination, but do require fairly strong inspiratory force (exactly how strong varies with the specific device). However, even asthma patients with reduced ventilatory volume can usually generate adequate inspiratory force, since the reduced volume primarily affects duration rather than force of inhalation (65).

Nebulizers convert a liquid solution or suspension into an aerosol using either a jet of compressed air or ultrasonic energy. The aerosol plume is then delivered to the patient through either a face mask or a mouthpiece. These devices make minimal demands on patient technique. Even with modern advances, however, they remain relatively bulky and are therefore typically prescribed only for patients unable to use either MDIs or DPIs. A systematic review has found that nebulizers appear at least as effective for ICS delivery as MDIs with large-volume spacers (66).

Delivered particle size is an important consideration in choice of an inhaler. Particles should ideally be between 1 and 5 μm in diameter, because larger particles are likely to be deposited in the oropharynx while very small particles will either be deposited in the upper airways or, if drawn into the lower airways, will be exhaled (67). Since replacement of CFCs by HFAs as the propellant required MDI redesign, many manufacturers utilized the opportunity to optimize design in other respects as well. Thus, while an older CFC-driven MDI deposited only 4–7% of beclomethasone dipropionate leaving the device into the lungs, the newer HFA-driven inhaler deposits 55–60% (9). Older studies comparing DPIs with CFC-driven MDIs are therefore no longer meaningful. The HFA-driven fluticasone inhaler, however, was deliberately designed to have the same particle size distribution and lung deposition as the CFC-driven device in order to maintain dosage comparability. This inhaler already had a relatively fine particle size, however, with the proportion of particles <5 μm in diameter being considerably higher than that seen for the same drug delivered by the Diskhaler DPI (68).

Particle sizes delivered by DPIs also differ between devices. Because of the large number of different designs, however, generalizations are difficult and only a limited number of possible comparisons have been addressed. One review has concluded that the Turbuhaler delivers twice as much of the administered drug to the lung as does the Diskus (69), but the studies cited are complicated by delivery of different drugs from the two devices. Clinical results may be of more interest, especially when the same drug is being administered. One such study found that patients receiving beclomethasone dipropionate via the Diskhaler (similar but not identical to the Diskus) were more likely to have used little or no short-acting β-agonist than were those receiving the same drug via the Rotohaler (70). A comparison of budesonide delivered by Airmax or Turbuhaler found that patients using the Airmax demonstrated a nonsignficant trend toward greater improvement in airway hyper-responsiveness but with no difference in forced expiratory volume in 1 s, peak expiratory flow or symptoms (71). Turning to nebulizers, Dahlström *et al.* (72) found no difference in lung deposition of budesonide as a function of nominal dose for three different jet nebulizers [the Inhalierboy, the LC Jet Plus (Pari Gmbh, Starnberg, Germany) and the MA-2 (Clinova Medical AB, Malmo, Sweden)], although a larger fraction of the dose actually delivered by the Inhalierboy was deposited in the oropharynx.

Although early studies reported that the Turbuhaler delivered twice as much budesonide to the lungs as did a MDI (73), and that this was reflected in patients prescribed a Turbuhaler getting the same or greater benefit with half the dose (65), these studies were all done with the CFC-driven MDI. Current evidence indicates no clinical difference among the various devices (74). Specifically, no differences in effectiveness or safety were seen in relatively short-term randomized controlled trials, although oropharyngeal adverse effects were not examined. However, such studies typically require all enrolled patients to demonstrate an ability to use the device correctly and otherwise gloss over factors that may be important for individual patients. Thus, choosing the correct delivery method for a specific patient calls for knowledge of both the device and the patient. Aside from patient ability and willingness to use a given device, patient preference may also be a factor, as may the availability of a given delivery device for the drug of choice.

FUTURE DIRECTIONS

Only a limited number of pathways toward safer and more effective ICS are available. Because therapeutic and adverse effects are exerted through the same receptor, greater selectivity through structural modification is not an option. Recently introduced agents exhibit near-maximum first-pass metabolism and protein binding, so further improvement in those respects is likewise not an option. Furthermore, one of those recently introduced drugs, ciclesonide, is a prodrug that remains inactive in the oropharyngeal cavity and that also exhibits relatively prolonged pulmonary residence time.

Nevertheless, approaches to improved ICS are still available. One is so-called 'soft drugs' that are rapidly inactivated on leaving the desired site of action. As ciclesonide's clearance exceeds hepatic blood flow, it could be considered a soft drug. There is no reason, however, to believe that ciclesonide's rate of extrahepatic metabolism is maximal, so room for improvement presumably exists. Bodor & Buchwald (75) review approaches to development of soft corticosteroids and discuss several that are currently in development for asthma or are approved for other indications. These are predominately esters with inactive hydrolytic metabolites, with prolonged pulmonary residence time being the primary approach to achieve the desired pulmonary selectivity. A more intuitively attractive approach would be to look for drugs metabolized by enzymes present in the bloodstream but not in the lung. This appears to be true of glucocorticoid γ-lactones metabolized by paraoxonase, but reports suggest that such compounds may have proven unsatisfactory.

It has also been suggested that compounds might be developed that selectively activate the glucocorticoid receptor so as to transrepress pro-inflammatory transcription factors such as NF-κB and AP-1 without promoting transcription of genes with glucocorticoid response elements (76). Attempts to develop such compounds have had limited success, however, and it is not even clear that such selective activation is possible.

CONCLUSION

Although ICS remain the accepted initial therapy for persistent asthma, safety concerns persist. These concerns are especially significant when it becomes desirable to escalate the dose beyond those usually recommended. Cataracts and loss of bone mineral density may be especially significant. Suppression of the HPA axis is often seen but becomes clinically significant, at least in adults, only at extremely high doses. Recent developments have eased some of these concerns, as newer ICS have essentially zero oral bioavailability and exhibit 98–99% binding to serum proteins. Some are also prodrugs that remain inactive in the oropharynx and therefore do not produce local adverse effects. Successful efforts to improve delivery devices are also ongoing. With further research, safer or even virtually risk-free ICS may be anticipated.

ACKNOWLEDGEMENTS

This study was supported by National Institutes of Health Grant HL070068 (to R.C.R.).

REFERENCES

1. Crompton G (2006) A brief history of inhaled asthma therapy over the last fifty years. *Primary Care Respiratory Journal*, **15,** 326–331.
2. Cameron SJ, Cooper EJ, Crompton GK, Hoare MV, Grant IW (1973) Substitution of beclomethasone aerosol for oral prednisolone in the treatment of chronic asthma. *British Medical Journal*, **4,** 205–207.
3. Hodson ME, Batten JC, Clarke SW, Gregg I (1974) Beclomethasone dipropionate aerosol in asthma. Transfer of steroid-dependent asthmatic patients from oral prednisone to beclomethasone dipropionate aerosol. *The American Review of Respiratory Disease*, **110,** 403–408.
4. Vilsvik JS, Schaanning J (1974) Beclomethasone dipropionate aerosol in adult steroid-dependent obstructive lung disease. *Scandinavian Journal of Respiratory Disease*, **55,** 169–175.
5. National Heart Lung and Blood Institute (2007) *Guidelines for the diagnosis and management of asthma*. Bethesda, MD: National Institutes of Health, US Department of Health and Human Services.
6. Adcock IM, Ito K (2004) Steroid resistance in asthma: a major problem requiring novel solutions or a non-issue? *Current Opinion in Pharmacology*, **4,** 257–262.
7. Barnes PJ (2006) Corticosteroids: the drugs to beat. *European Journal of Pharmacology*, **533,** 2–14.
8. Chanez P, Wenzel SE, Anderson GP *et al.* (2007) Severe asthma in adults: what are the important

questions? *Journal of Allergy and Clinical Immunology*, **119,** 1337–1348.
9. Leach CL, Davidson PJ, Boudreau RJ (1998) Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *European Respiratory Journal*, **12,** 1346–1353.
10. Willey RF, Milne LJ, Crompton GK, Grant IW (1976) Beclomethasone dipropionate aerosol and oropharyngeal candidiasis. *British Journal of Diseases of the Chest*, **70,** 32–38.
11. Kennedy WA, Laurier C, Gautrin D *et al.* (2000) Occurrence and risk factors of oral candidiasis treated with oral antifungals in seniors using inhaled steroids. *Journal of Clinical Epidemiology*, **53,** 696–701.
12. Roland NJ, Bhalla RK, Earis J (2004) The local side effects of inhaled corticosteroids: current understanding and review of the literature. *Chest*, **126,** 213–219.
13. Buhl R (2006) Local oropharyngeal side effects of inhaled corticosteroids in patients with asthma. *Allergy*, **61,** 518–526.
14. Selroos O, Backman R, Forsen KO *et al.* (1994) Local side-effects during 4-year treatment with inhaled corticosteroids – a comparison between pressurized metered-dose inhalers and Turbuhaler. *Allergy*, **49,** 888–890.
15. Williamson IJ, Matusiewicz SP, Brown PH, Greening AP, Crompton GK (1995) Frequency of voice problems and cough in patients using pressurized aerosol inhaled steroid preparations. *European Respiratory Journal*, **8,** 590–592.
16. Dubus J-C, Mely L, Huiart L, Marguet C, Le Roux P (2003) Cough after inhalation of corticosteroids delivered from spacer devices in children with asthma. *Fundamental and Clinical Pharmacology*, **17,** 627–631.
17. Lipworth BJ (1999) Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Archives of Internal Medicine*, **159,** 941–955.
18. Weiner P, Berar-Yanay N, Davidovich A, Magadle R (1999) Nocturnal cortisol secretion in asthmatic patients after inhalation of fluticasone propionate. *Chest*, **116,** 931–934.
19. Grahnen A, Eckernas SA, Brundin RM, Ling-Andersson A (1994) An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *British Journal of Clinical Pharmacology*, **38,** 521–525.
20. White M, Crisalida T, Li H, Economides A, Kaliner M (2006) Effects of long-term inhaled corticosteroids on adrenal function in patients with asthma. *Annals of Allergy, Asthma, and Immunology*, **96,** 437–444.
21. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D (2002) Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Archives of Disease in Childhood*, **87,** 457–461.
22. Autio P, Karjalainen J, Risteli L, Risteli J, Kiistala U, Oikarinen A (1996) Effects of an inhaled steroid (budesonide) on skin collagen synthesis of asthma patients in vivo. *American Journal of Respiratory and Critical Care Medicine*, **153,** 1172–1175.
23. Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY (1990) Purpura and dermal thinning associated with high dose inhaled corticosteroids. *British Medical Journal*, **300,** 1548–1551.
24. Tashkin DP, Murray HE, Skeans M, Murray RP (2004) Skin manifestations of inhaled corticosteroids in COPD patients: results from Lung Health Study II. *Chest*, **126,** 1123–1133.
25. Mak VH, Melchor R, Spiro SG (1992) Easy bruising as a side-effect of inhaled corticosteroids. *European Respiratory Journal*, **5,** 1068–1074.
26. Pauwels RA, Lofdahl CG, Laitinen LA *et al.* (1999) Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*, **340,** 1948–1953.
27. Roy A, Leblanc C, Paquette L *et al.* (1996) Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. *European Respiratory Journal*, **9,** 226–231.
28. Egan JJ, Maden C, Kalra S, Adams JE, Eastell R, Woodcock AA (1999) A randomized, double-blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. *European Respiratory Journal*, **13,** 1267–1275.
29. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S (1995) Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *Journal of Allergy and Clinical Immunology*, **96,** 571–579.
30. Herrala J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM (1994) Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. *Bone*, **15,** 621–623.
31. Marystone JF, Barrett-Connor EL, Morton DJ (1995) Inhaled and oral corticosteroids: their effects on bone mineral density in older adults. *American Journal of Public Health*, **85,** 1693–1695.
32. Kerstjens HA, Postma DS, van Doormaal JJ *et al.* (1994) Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in

patients with airways obstruction. Dutch CNSLD Study Group. *Thorax*, **49,** 652–656.
33. Pouw EM, Prummel MF, Oosting H, Roos CM, Endert E (1991) Beclomethasone inhalation decreases serum osteocalcin concentrations. *British Medical Journal*, **302,** 627–628.
34. Teelucksingh S, Padfield PL, Tibi L, Gough KJ, Holt PR (1991) Inhaled corticosteroids, bone formation, and osteocalcin. *Lancet*, **338,** 60–61.
35. Wong CA, Walsh LJ, Smith CJP *et al.* (2000) Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet*, **355,** 1399–1403.
36. Kelly HW, Nelson HS (2003) Potential adverse effects of the inhaled corticosteroids. *Journal of Allergy and Clinical Immunology*, **112,** 469–478 (quiz 79).
37. Rossi GA, Cerasoli F, Cazzola M (2007) Safety of inhaled corticosteroids: room for improvement. *Pulmonary Pharmacology & Therapeutics*, **20,** 23–35.
38. Tattersfield AE, Harrison TW, Hubbard RB, Mortimer K (2004) Safety of inhaled corticosteroids. *Proceedings of the American Thoracic Society*, **1,** 171–175.
39. Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G (2002) Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. *Cochrane database of systematic reviews (Online)*, CD003537.
40. Toogood JH, Markov AE, Baskerville J, Dyson C (1993) Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. *Journal of Allergy and Clinical Immunology*, **91,** 571–579.
41. Cumming RG, Mitchell P, Leeder SR (1997) Use of inhaled corticosteroids and the risk of cataracts. *New England Journal of Medicine*, **337,** 8–14.
42. Smeeth L, Boulis M, Hubbard R, Fletcher AE (2003) A population based case–control study of cataract and inhaled corticosteroids. *British Journal of Ophthalmology*, **87,** 1247–1251.
43. Uboweja A, Malhotra S, Pandhi P (2006) Effect of inhaled corticosteroids on risk of development of cataract: a meta-analysis. *Fundamental and Clinical Pharmacology*, **20,** 305–309.
44. Garbe E, LeLorier J, Boivin JF, Suissa S (1997) Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA*, **277,** 722–727.
45. Samiy N, Walton DS, Dreyer EB (1996) Inhaled steroids: effect on intraocular pressure in patients without glaucoma. *Canadian Journal of Ophthalmology*, **31,** 120–123.
46. Sin DD, Tu JV (2001) Inhaled corticosteroid therapy reduces the risk of rehospitalization and all-cause mortality in elderly asthmatics. *European Respiratory Journal*, **17,** 380–385.
47. Ryrfeldt A, Andersson P, Edsbacker S, Tonnesson M, Davies D, Pauwels R (1982) Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *European Journal of Respiratory Diseases. Supplement*, **122,** 86–95.
48. Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N (2001) Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. *British Journal of Clinical Pharmacology*, **51,** 400–409.
49. Derendorf H (2007) Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. *Journal of Clinical Pharmacology*, **47,** 782–789.
50. Thorsson L, Dahlström K, Edsbäcker S, Kallén A, Paulson J, Wirén JE (1997) Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects. *British Journal of Clinical Pharmacology*, **43,** 155–161.
51. Nave R, Bethke TD, van Marle SP, Zech K (2004) Pharmacokinetics of [14C]ciclesonide after oral and intravenous administration to healthy subjects. *Clinical Pharmacokinetics*, **43,** 479–486.
52. Hübner M, Hochhaus G, Derendorf H (2005) Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids. *Immunology and allergy clinics of North America*, **25,** 469–488.
53. Tunek A, Sjodin K, Hallstrom G (1997) Reversible formation of fatty acid esters of budesonide, an antiasthma glucocorticoid, in human lung and liver microsomes. *Drug Metabolism and Disposition*, **25,** 1311–1317.
54. Hubbard WC, Blum AE, Bickel CA, Heller NM, Schleimer RP (2003) Detection and quantitation of fatty acid acyl conjugates of triamcinolone acetonide via gas chromatography–electron-capture negative-ion mass spectrometry. *Analytical Biochemistry*, **322,** 243–250.
55. Nave R, Meyer W, Fuhst R, Zech K (2005) Formation of fatty acid conjugates of ciclesonide active metabolite in the rat lung after 4-week inhalation of ciclesonide. *Pulmonary Pharmacology & Therapeutics*, **18,** 390–396.
56. Mutch E, Nave R, McCracken N, Zech K, Williams FM (2007) The role of esterases in the metabolism of ciclesonide to desisobutyryl-ciclesonide in human tissue. *Biochemical Pharmacology*, **73,** 1657–1664.
57. Rohatagi S, Arya V, Zech K *et al.* (2003) Population pharmacokinetics and pharmacodynamics of ciclesonide. *Journal of Clinical Pharmacology*, **43,** 365–378.

58. Adams N, Bestall J, Jones PW (2001) Budesonide at different doses for chronic asthma. *Cochrane database of systematic reviews (Online)*, CD003271.
59. Adams NP, Jones PW (2006) The dose-response characteristics of inhaled corticosteroids when used to treat asthma: an overview of Cochrane systematic reviews. *Respiratory Medicine*, **100,** 1297–1306.
60. Bateman E, Karpel J, Casale T, Wenzel S, Banerji D (2006) Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. *Chest*, **129,** 1176–1187.
61. Meltzer EO, Wenzel S (2006) The efficacy and safety of mometasone furoate delivered via a dry powder inhaler for the treatment of asthma. *Journal of Asthma*, **43,** 765–772.
62. Fish JE, Karpel JP, Craig TJ *et al.* (2000) Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. *Journal of Allergy and Clinical Immunology*, **106,** 852–860.
63. Larsen JS, Hahn M, Ekholm B, Wick KA (1994) Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *Journal of Asthma*, **31,** 193–199.
64. Guidry GG, Brown WD, Stogner SW, George RB (1992) Incorrect use of metered dose inhalers by medical personnel. *Chest*, **101,** 31–33.
65. Thorsson L, Geller D (2005) Factors guiding the choice of delivery device for inhaled corticosteroids in the long-term management of stable asthma and COPD: focus on budesonide. *Respiratory Medicine*, **99,** 836–849.
66. Cates CJ, Bestall J, Adams N (2006) Holding chambers versus nebulisers for inhaled steroids in chronic asthma. *Cochrane database of systematic reviews (Online)*, CD001491.
67. Dolovich MB (2002) Aeorsol delivery devices and airways/lung deposition. In: Schleimer RP, O'Byrne PM, Szefler SJ, Brattsand R, eds. *Aeorsol delivery devices and airways/*lung deposition. Basel: Marcel Dekker, 169–212.
68. Olsson B (1995) Aerosol particle generation from dry powder inhalers: can they equal pressurized metered dose inhalers? *Journal of Aerosol Medicine*, **8**(Suppl. 3)**,** S13–S18 (discussion S19).
69. Borgström L, Asking L, Thorsson L (2005) Idealhalers or realhalers? A comparison of Diskus and Turbuhaler. *International Journal of Clinical Practice*, **59,** 1488–1495.
70. Thomas M, Williams AE (2005) Are outcomes the same with all dry powder inhalers? *International Journal of Clinical Practice*, **59** (Suppl 149)**,** 33–35.
71. Frew AJ, Langley SJ, Perrin V, Hertog MG (2002) Effects of 4-week treatment with low-dose budesonide (100 micrograms BID) from a novel inhaler Airmax and from a conventional inhaler on bronchial hyper-responsiveness, lung function and symptoms in patients with mild asthma. *Respiratory Medicine*, **96,** 542–547.
72. Dahlström K, Thorsson L, Larsson P, Nikander K (2003) Systemic availability and lung deposition of budesonide via three different nebulizers in adults. *Annals of Allergy, Asthma, and Immunology*, **90,** 226–232.
73. Thorsson L, Edsbacker S, Conradson TB (1994) Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *European Respiratory Journal*, **7,** 1839–1844.
74. Dolovich MB, Ahrens RC, Hess DR *et al.* (2005) Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest*, **127,** 335–371.
75. Bodor N, Buchwald P (2006) Corticosteroid design for the treatment of asthma: structural insights and the therapeutic potential of soft corticosteroids. *Current Pharmaceutical Design*, **12,** 3241–3260.
76. Biggadike K, Uings I, Farrow SN (2004) Designing corticosteroid drugs for pulmonary selectivity. *Proceedings of the American Thoracic Society*, **1,** 352–355.
77. Dickens GR, Wermeling DP, Matheny CJ *et al.* (2000) Pharmacokinetics of flunisolide administered via metered dose inhaler with and without a spacer device and following oral administration. *Annals of Allergy, Asthma, and Immunology*, **84,** 528–532.
78. Mollmann H, Wagner M, Krishnaswami S *et al.* (2001) Single-dose and steady-state pharmacokinetic and pharmacodynamic evaluation of therapeutically clinically equivalent doses of inhaled fluticasone propionate and budesonide, given as Diskus or Turbohaler dry-powder inhalers to healthy subjects. *Journal of Clinical Pharmacology*, **41,** 1329–1338.
79. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W (2006) Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *European Respiratory Journal*, **28,** 1042–1050.
80. Crim C, Pierre LN, Daley-Yates PT (2001) A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. *Clinical Therapeutics*, **23,** 1339–1354.
81. Tayab ZR, Fardon TC, Lee DKC *et al.* (2007) Pharmacokinetic/pharmacodynamic evaluation of urinary cortisol suppression after inhalation of fluticasone propionate and mometasone furoate. *British Journal of Clinical Pharmacology*, **64,** 698–705.
82. Valotis A, Neukam K, Elert O, Högger P (2004) Human receptor kinetics, tissue binding affinity, and

stability of mometasone furoate. *Journal of Pharmaceutical Sciences*, **93,** 1337–1350.
83. Belvisi MG, Bundschuh DS, Stoeck M *et al*. (2005) Preclinical profile of ciclesonide, a novel corticosteroid for the treatment of asthma. *Journal of Pharmacology and Experimental Therapeutics*, **314,** 568–574.
84. Jaffuel D, Demoly P, Gougat C *et al*. (2000) Transcriptional potencies of inhaled glucocorticoids. *American Journal of Respiratory and Critical Care Medicine*, **162,** 57–63.