

## Artigo original

# Corticosteroid Therapy for Asthma

## Corticoterapia no Tratamento da Asma

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### RESUMO

Os corticosteroides são os mais efetivos controladores da asma. Eles suprimem a inflamação, principalmente através da inativação de múltiplos genes inflamatórios ativos através da reversão da acetilação da histona via recrutamento da histona desacetilase 2. Suprimindo a inflamação da via aérea, os corticosteroides inalatórios (CSI) reduzem a hiper-responsividade brônquica e controlam os sintomas da asma.

Atualmente, os CSI representam a primeira linha de tratamento para todos os pacientes com asma persistente, controlando os sintomas e prevenindo as exacerbações. A associação de  $\beta_2$ -agonistas de longa duração aos CSI aumenta o controle da asma e, habitualmente, ambos são administrados em um mesmo dispositivo inalatório, o que aumenta a adesão e o controle da asma com menores doses. A absorção dos CSI dos pulmões para a circulação sistêmica causa efeitos colaterais sistêmicos desprezíveis nas doses que a maioria dos doentes requer. Corticosteroides sistêmicos são usados no tratamento das exacerbações agudas da asma e como tratamento de manutenção em pacientes com asma grave não controlada com a terapia inalatória máxima. Corticosteroides orais têm numerosos efeitos colaterais metabólicos e endócrinos e devem ser usados na menor dose necessária para controlar a doença.

**Descritores:** Inflamação; Histona desacetilases; Asma/prevenção & controle; Agonistas de receptores adrenérgicos beta 2; Córtex supra-renal/efeitos de drogas.

### ABSTRACT

Corticosteroids are by far the most effective controllers of asthma. They suppress inflammation mainly by switching off multiple activated inflammatory genes, which is achieved by reversing histone acetylation via the recruitment of histone deacetylase 2. Through suppression of airway inflammation, inhaled corticosteroids (ICS) reduce airway hyperresponsiveness and control asthma symptoms.

The use of ICS, which is now recommended as the first-line therapy for all patients with persistent asthma, controls asthma symptoms and prevents exacerbations. Inhaled long-acting  $\beta_2$  agonists added to ICS further improve asthma control and are commonly given as combination inhalers, which improve compliance and control asthma at lower doses. The use of ICS, which are absorbed from the lungs into the systemic circulation, has negligible systemic side effects at the doses most patients require. Systemic corticosteroids are used in the treatment of acute exacerbations of asthma and as maintenance therapy in patients with severe asthma that is not controlled by the maximum dose of ICS. Oral steroids have numerous metabolic and endocrine side effects. Therefore, the lowest dose needed to control the disease should be used.

**Keywords:** Inflammation; Histone deacetylases; Asthma/prevention & control; Adrenergic beta-2 receptor agonists; Adrenal cortex/drug effects.

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The authors declare that they do not have any potential conflict of interest.

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## INTRODUCTION

Corticosteroids (also known as glucocorticosteroids, glucocorticoids, and steroids) are by far the most effective controllers used in the treatment of asthma and the only drugs that can effectively suppress the characteristic inflammation in asthmatic airways. After discussing the mechanism of action and pharmacology of corticosteroids, I will discuss their use in the treatment of asthma.

## MECHANISMS OF ACTION

There have been major advances in understanding the molecular mechanisms whereby corticosteroids suppress inflammation, based on recent developments in understanding the fundamental mechanisms of gene transcription (1,2). Corticosteroids activate or suppress many genes relevant to understanding their action in asthma.

### Cellular effects

At a cellular level, corticosteroids reduce the numbers of inflammatory cells in the airways, including eosinophils, T lymphocytes, mast cells and dendritic cells (Figure 1). This is achieved by inhibiting the recruitment of inflammatory cells into the airway by suppressing the production of chemotactic mediators and adhesion molecules and by inhibiting the survival in the airways of inflammatory cells, such as eosinophils, T lymphocytes and mast cells. Epithelial cells might be the major cellular target for inhaled corticosteroids (ICS), which are the mainstay of modern asthma management. The ICS suppress many activated inflammatory genes in airway epithelial cells and epithelial integrity is restored by regular ICS therapy. The suppression of mucosal inflammation is relatively rapid with a significant reduction in eosinophils detectable within 6 h and associated with reduced airway hyperresponsiveness (3). Reversal of airway hyperresponsiveness

may take several months to reach a plateau, probably reflecting recovery of structural changes in the airway.

### Glucocorticoid receptors

Corticosteroids diffuse across the cell membrane and bind to glucocorticoid receptors (GRs) in the cytoplasm. There is only one form of GR that binds corticosteroids, termed GR $\alpha$ . An alternatively spliced form of GR that interacts with DNA but not with corticosteroids is GR $\beta$ , which could act as a dominant negative inhibitor of corticosteroid action by interfering with the binding of GR to DNA (4). Whether GR $\beta$  is involved in steroid resistance in asthma is controversial. Activated GRs rapidly translocate to the nucleus, where they produce their molecular effects. A GR pair (GR dimer) binds to glucocorticoid response elements in the promoter region of steroid-responsive genes and this interaction switches on (and sometimes switches off) gene transcription. Examples of genes that are activated by corticosteroids include genes encoding  $\beta_2$ -adrenergic receptors and the anti-inflammatory proteins secretory leukoprotease inhibitor and mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1) which inhibits MAP kinase pathways. These effects may contribute to the anti-inflammatory actions of corticosteroids. Interaction between GRs and negative glucocorticoid response elements could suppress gene transcription, and this is thought to be important in mediating many of the side effects of corticosteroids. For example, corticosteroids inhibit the expression of osteocalcin, which is involved in bone synthesis (5).

### Switching off inflammation

The major action of corticosteroids is to switch off multiple activated inflammatory genes that encode for cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors (2). These genes are switched on in the airways by pro-inflammatory transcription factors, such as nuclear factor kappa B (NF- $\kappa$ B) and activator protein-1, both of which are activated in asthmatic airways and switch on inflammatory genes by interacting with co-activator molecules, such as cAMP response element binding protein-binding protein, that have intrinsic histone acetyltransferase activity, resulting in acetylation of core histones, which opens up the chromatin structure so that gene transcription is facilitated. Corticosteroid-activated GRs also interact with co-activator molecules, and this inhibits the interaction of NF- $\kappa$ B with co-activators, thus reducing histone acetylation (6,7). Reduction of histone acetylation also

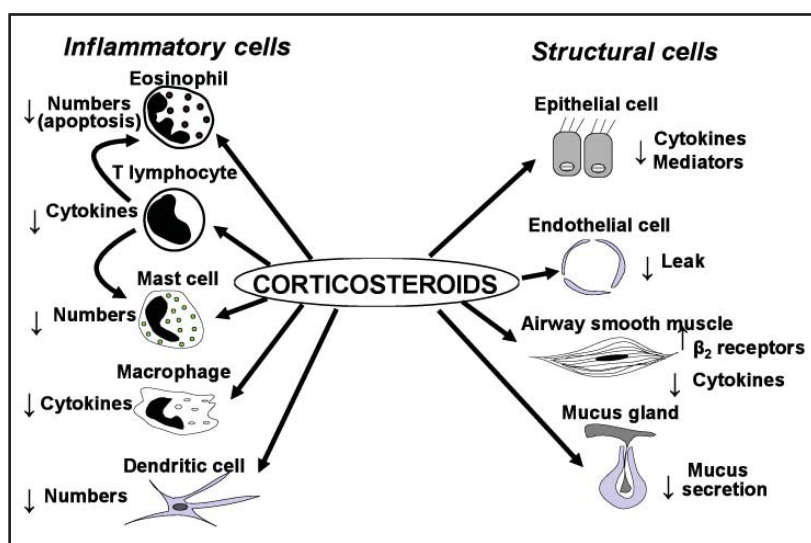


Figure 1 - Cellular effect of corticosteroids.

occurs through the recruitment of histone deacetylase 2 to the activated inflammatory gene complex by activated GRs, resulting in effective suppression of all activated inflammatory genes within the nucleus

(Figure 2). This explains why corticosteroids are so effective in the control of asthmatic inflammation but also why they are safe, because other activated genes are not affected.

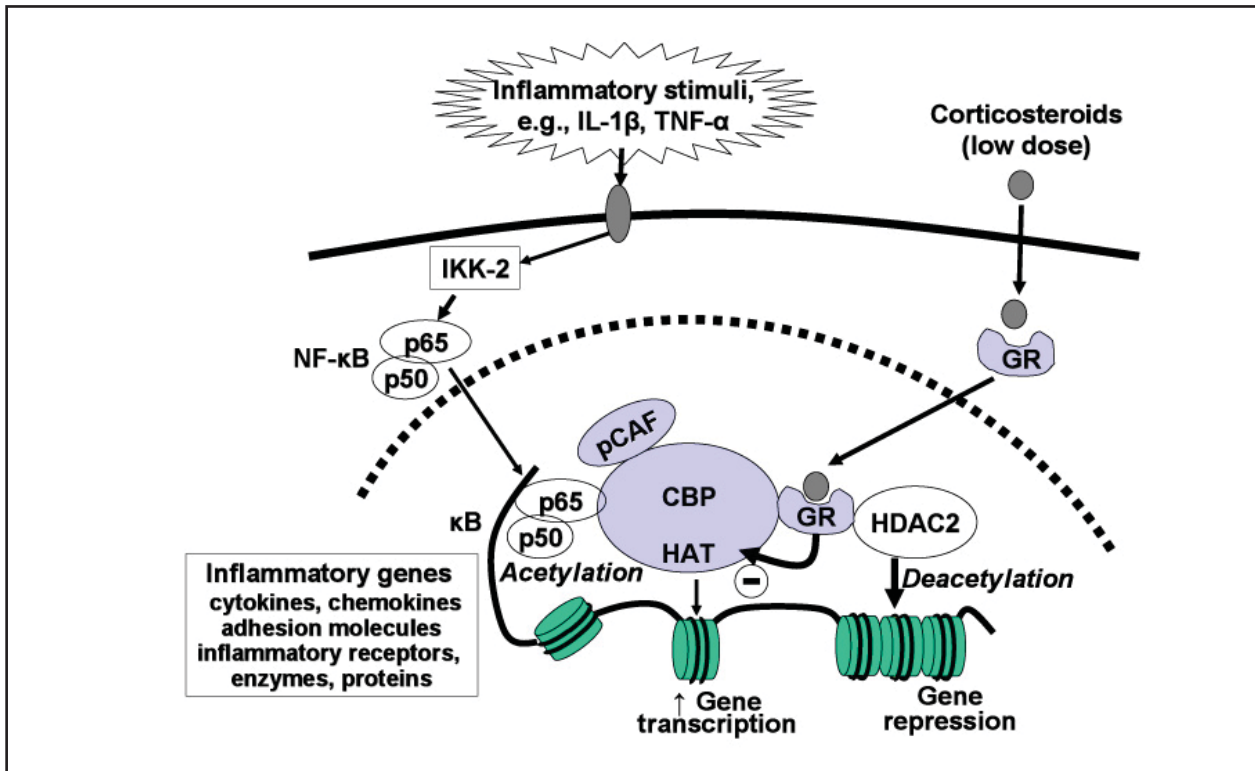


Figure 2 - Corticosteroid suppression of activated inflammatory genes. Inflammatory genes are activated by inflammatory stimuli, such as IL-1 $\beta$  and TNF- $\alpha$ , resulting in activation of the I- $\kappa$ B kinase-2 (IKK-2) inhibitor, which activates the transcription factor NF- $\kappa$ B. A dimer of the p50 and p65 NF- $\kappa$ B proteins translocates to the nucleus and binds to specific  $\kappa$ B recognition sites and to co-activators, such as the cAMP response element binding protein-binding protein (CBP) or p300/CBP-activating factor (pCAF), which have intrinsic histone acetyltransferase (HAT) activity. This results in acetylation of core histone H4, resulting in increased expression of genes encoding multiple inflammatory proteins. After activation by corticosteroids, GRs translocate to the nucleus and bind to co-activators to inhibit HAT activity directly and recruiting histone deacetylase-2 (HDAC2), which reverses histone acetylation leading to suppression of these activated inflammatory genes.

There could be additional mechanisms that are important in the anti-inflammatory actions of corticosteroids. Corticosteroids have potent inhibitory effects on MAP kinase signalling pathways through the induction of MKP-1, and this could inhibit the expression of multiple inflammatory genes (8). Some inflammatory genes, such as granulocyte-macrophage colony stimulating factor, have an unstable messenger RNA that is rapidly degraded by certain RNases but stabilised when cells are stimulated by inflammatory mediators. Corticosteroids reverse this effect, resulting in rapid degradation of mRNA and reduced inflammatory protein secretion (9).

#### INTERACTION WITH $\beta_2$ -ADRENERGIC RECEPTORS

Inhaled  $\beta_2$  agonists and corticosteroids are frequently used together in the control of asthma. Figure 3 shows the important molecular interactions between these two classes of drugs (10). As discussed above, corticosteroids increase the gene transcription of  $\beta_2$  receptors, resulting in increased expression of cell

surface receptors. This has been demonstrated in human lung *in vitro* and nasal mucosa *in vivo* (after topical application). Thus, corticosteroids protect against the downregulation of  $\beta_2$  receptors after long-term administration of  $\beta_2$  agonists. This could be important for the non-bronchodilator effects of  $\beta_2$  agonists, such as mast cell stabilization. Corticosteroids might also enhance the coupling of  $\beta_2$  receptors to G proteins, thus enhancing  $\beta_2$  agonist effects and reversing the uncoupling of  $\beta_2$  receptors that can occur in response to inflammatory mediators, such as interleukin-1 $\beta$  through a stimulatory effect on a G protein-coupled receptor kinase.

There is evidence that  $\beta_2$  agonists affect GR function and thus enhance the anti-inflammatory effects of corticosteroids. In addition,  $\beta_2$  agonists increase the translocation of GR from cytoplasm to the nucleus after activation by corticosteroids. This effect has now been demonstrated in sputum macrophages of asthma patients after an ICS and inhaled long-acting  $\beta_2$  agonist (11). This suggests that  $\beta_2$  agonists and corticosteroids enhance each other's beneficial effects in asthma therapy.

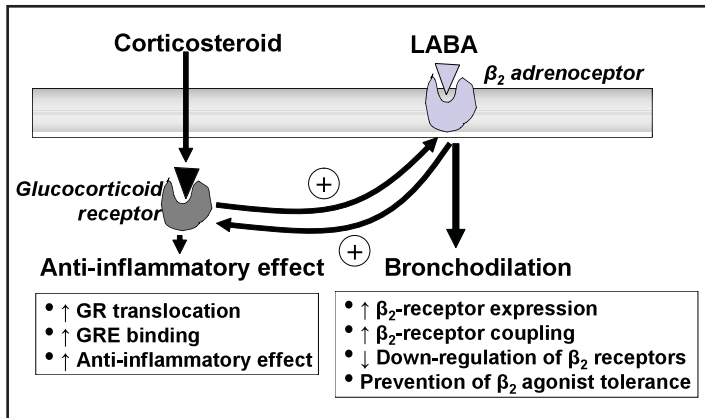


Figure 3 - Molecular interaction between corticosteroids and  $\beta_2$  agonists  
LABA: long-acting  $\beta_2$  agonist; GRE: glucocorticoid response element.

**PHARMACOKINETICS**

Prednisolone is readily and consistently absorbed after oral administration with little inter-individual variation. Prednisone is converted in the liver to active prednisolone. Drugs such as rifampin, phenobarbitone, and phenytoin, which induce CYP450 enzymes, lower the plasma half-life of prednisolone, which is metabolized in the liver. The plasma half-life of prednisolone is 2-3 h, although its biological half-life is approximately 24 h, making it suitable for daily dosing. Prednisolone is approximately 92% protein-bound, the majority to the specific binding protein transcortin and the remainder to albumin; it is the unbound fraction that is biologically active. Certain patients, typically those with severe asthma, apparently fail to respond to corticosteroids. "Steroid-resistant" asthma is caused not by impaired absorption or metabolism of steroids but rather by reduced anti-inflammatory actions of corticosteroids. Measurement of plasma concentrations of prednisolone are useful in monitoring compliance with oral corticosteroid therapy and in assessing whether a poor therapeutic response to corticosteroids is due to poor absorption or increased metabolism.

**Inhaled delivery**

The pharmacokinetics of ICS is important in relation to their systemic effects (12). The fraction of steroid which is inhaled into the lungs acts locally on the airway mucosa but can be absorbed from the airway and alveolar surface. That fraction therefore reaches the systemic circulation (Figure 4). The fraction of ICS that is deposited in the oropharynx is swallowed and absorbed from the gut. The absorbed fraction can be metabolized in the liver before reaching the systemic circulation (first-pass metabolism). Budesonide and fluticasone propionate have a greater first-pass metabolism than does beclomethasone dipropionate and are therefore less likely to produce systemic effects at high inhaled doses. The use of a large-volume spacer

reduces oropharyngeal deposition, thereby reducing the systemic absorption of corticosteroids, although this effect is minimal in corticosteroids with a high first-pass metabolism. Mouth rinsing has a similar effect, and this procedure should be used with high-dose dry powder inhalers, because spacers cannot be used with these devices.

A recently introduced corticosteroid, ciclesonide, is an inactive prodrug that is activated by esterases in the lung to the active metabolite desisobuteryl-ciclesonide (13). This could reduce oropharyngeal side effects, as esterases appear to be less active at this site than in the lower airways. Ciclesonide is also reported to be effective as a once-daily therapy.

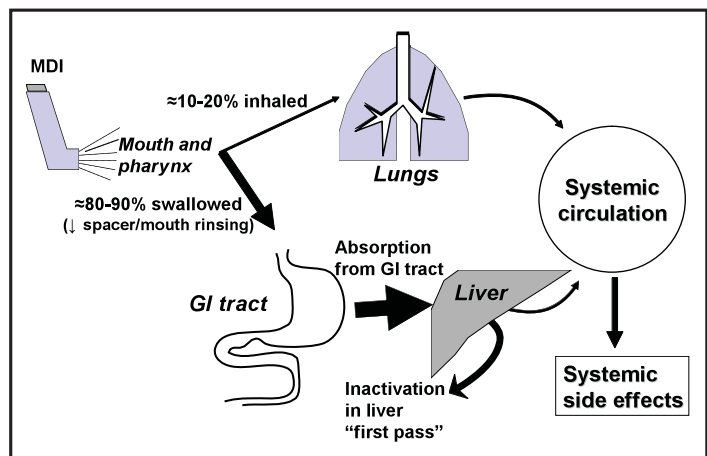


Figure 4 - Pharmacokinetics of inhaled corticosteroids.  
GI: gastrointestinal.

**SYSTEMIC STEROIDS**

There is no apparent advantage in giving very high doses of intravenous steroids (such as methylprednisolone at 1 g), as this only increases the risk of side effects, such as hyperglycaemia and increased susceptibility to infections. Intravenous steroids are indicated in acute asthma if lung function is < 30% of predicted and if there is no significant improvement with a nebulised  $\beta_2$  agonist. Oral prednisolone (40-60 mg) has an effect similar to that of intravenous hydrocortisone and is easier to administer. High doses of ICS can also substitute for a course of oral steroids in controlling acute exacerbations of asthma. In a family practice setting and in children in an emergency room setting, high-dose fluticasone propionate (2,000  $\mu$ g daily) was found to be as effective as was a course of oral prednisolone in controlling acute exacerbations of asthma, although this route of delivery is more costly (14). Although doubling the dose of ICS has been recommended for mild exacerbations of asthma, this does not appear to be useful (15). Although there is no proven effect of ICS in the management of severe acute asthma in a hospital setting (16), trials of nebulized steroids, which can be delivered in large doses, are underway.

Maintenance treatment with oral steroids is reserved for patients in whom asthma cannot be controlled with the maximum doses of other drugs, the dose being titrated to the lowest that provides acceptable control of symptoms. For any patient taking regular oral steroids, objective evidence of steroid responsiveness should be obtained before maintenance therapy is instituted. Short courses of oral steroids (30-40 mg of prednisolone daily for 1-2 weeks) are indicated for exacerbations of asthma, and the dose can be tapered over 1 week once the exacerbation is resolved (although the tapering period is not strictly necessary, patients often find it reassuring).

### INHALED CORTICOSTEROIDS

There is no doubt that the early use of ICS has revolutionized the management of asthma, with marked reductions in asthma morbidity and improvement in health status. Currently, ICS are recommended as the first-line therapy for all patients with persistent asthma (17) and are highly effective in controlling asthma symptoms in patients of all ages and with any degree of asthma severity. These drugs improve the quality of life of patients with asthma, allowing many patients to lead normal lives, as well as improving lung function, reducing the frequency of exacerbations, and potentially preventing irreversible airway changes.

The use of ICS is as effective in children, including young children, as in adults. Nebulized budesonide has been shown to reduce the need for oral corticosteroids and improve lung function in children under 3 years of age (18). In infants and preschool children, ICS given via a large-volume spacer device improve asthma symptoms and reduce the number of exacerbations.

Some patients with asthma develop an element of irreversible airflow obstruction, which could be the result of chronic airway inflammation and could be prevented by treatment with ICS. A 5-year study of low-dose budesonide in patients with mild asthma showed improved lung function after ICS therapy (19). A delay in starting ICS can result in less overall improvement in lung function, in adults and children (20,21). However, there is no evidence that early use of ICS is curative. Even when ICS therapy is introduced at the time of diagnosis, symptoms and lung function revert to pre-treatment levels when ICS are withdrawn (20).

A retrospective review of the risk of mortality and prescribed anti-asthma medication showed that regular ICS therapy provided significant protection (22). In contrast, asthma mortality appears to increase with increasing usage of short-acting  $\beta_2$  agonists, reflecting the fact that increased use of rescue medications is a marker of poor asthma control (23).

As previously mentioned, ICS are now recommended as first-line therapy for patients with persistent symptoms. Any patient who needs to use a  $\beta_2$  agonist inhaler for symptom control more than

twice a week should be started on ICS. Once control (defined as normal or best possible lung function and infrequent need to use an inhaled  $\beta_2$  agonist) has been achieved, the dose of ICS should be reduced in a step-wise manner to the lowest dose needed for optimal control. It might take as long as three months to reach a response plateau, and any subsequent changes in dose should be made at intervals of three months or more. When daily doses of  $\geq 800 \mu\text{g}$  are needed, patients should use a large-volume spacer device (for metered dose inhalers) or mouth rinsing (for dry powder inhalers), in order to reduce local and systemic side effects. Although the dose of ICS should be increased to 2,000  $\mu\text{g}$  daily if necessary, higher doses can have systemic effects. It may be preferable to add a low dose of oral corticosteroid, since higher doses of ICS are costly and have a high incidence of local side effects. Nebulized budesonide has been advocated in order to give an increased dose of ICS and to reduce the requirement for oral corticosteroids (24). However, that treatment is expensive and likely achieves its effects largely via systemic absorption.

### Add-on therapy

Previously, it was recommended that the ICS dose be increased if asthma was not controlled. The assumption was that there was residual inflammation of the airways. However the dose-response effect of ICS is relatively flat, so that there is little improvement in lung function after increasing the dose of ICS. An alternative strategy is to add some other class of controller drug. For most patients, that is more effective than is increasing the dose of ICS (25).

Many studies have demonstrated the great efficacy of using an ICS-long-acting  $\beta_2$  agonist combination, in comparison with using higher doses of a long-acting  $\beta_2$  agonist or higher doses of an ICS (26). Recent studies have shown that combining formoterol with budesonide (as reliever therapy) provides better asthma control than does the standard regimen of using a short-acting  $\beta_2$  agonist as a rescue medication with either the same dose of combination inhaler or a high dose of ICS as maintenance treatment (27). The mechanism by which ICS (used as needed) improve asthma control and reduce exacerbations is likely to involve preventing the increase in inflammation that occurs prior to a clinical exacerbation (28).

The addition of low doses of theophylline (achieving plasma concentrations of  $< 10 \text{ mg/L}$ ) are more effective than is doubling the dose of inhaled budesonide, regardless of the degree of asthma severity (29-31). However, this is less effective than is using a long-acting inhaled  $\beta_2$  agonist as add-on therapy (32). Anti-leukotrienes have also been used as an add-on therapy (33,34), although this is also less effective than is the addition of a long-acting  $\beta_2$  agonist (35).

## SIDE EFFECTS

The efficacy of ICS is now established in short- and long-term studies of adults and children. However, there are still concerns about side effects, particularly in children and when high inhaled doses are used. A number of side effects have been recognized (Chart 1).

Chart 1 - Side effects of inhaled corticosteroids

<p><b>Local side effects</b></p> <ul style="list-style-type: none"> <li>Dysphonia</li> <li>Oropharyngeal candidiasis</li> <li>Cough</li> </ul> <p><b>Systemic side effects</b></p> <ul style="list-style-type: none"> <li>Adrenal suppression</li> <li>Growth suppression</li> <li>Bruising</li> <li>Osteoporosis</li> <li>Cataracts</li> <li>Glaucoma</li> <li>Metabolic abnormalities (glucose, insulin, triglycerides)</li> <li>Psychiatric disturbances</li> </ul>
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### Local side effects

Although side effects due to the local deposition of ICS in the oropharynx might occur, the frequency of complaints depends on the dose and frequency of administration, as well as on the delivery system used. The most common complaint is of hoarseness (dysphonia), which occurs in over 50% of patients using metered dose inhalers. Dysphonia can be caused by myopathy of laryngeal muscles and can reverse when treatment is withdrawn. For most patients, dysphonia is not troublesome, although it can be disabling in singers and lecturers. With concomitant oral corticosteroids and more than twice daily administration, oropharyngeal candidiasis (thrush) can be a problem in some patients, par-

ticularly in elderly patients. Large-volume spacer devices protect against this local side effect by reducing the quantity of ICS that deposits in the oropharynx.

### Systemic side effects

Systemic side effects of ICS have been extensively investigated. Effects such as cataract formation and osteoporosis have been reported, although often in patients who are also receiving oral corticosteroids. There has been particular concern about growth suppression in children using ICS. However, in most studies, doses of 400 µg or less have not been associated with impaired growth, and there might even be a growth spurt because asthma is better controlled.

Pharmacokinetics are important. The fraction of corticosteroid inhaled into the lungs acts locally on the airway mucosa and can be absorbed from the airway and alveolar surface, thereby reaching the systemic circulation. The fraction of ICS deposited in the oropharynx is swallowed and absorbed from the gut. The absorbed fraction can be metabolized in the liver before it reaches the systemic circulation. Budesonide and fluticasone have a greater first-pass metabolism than does beclomethasone dipropionate and are therefore less likely to produce systemic effects at high inhaled doses. The use of a spacer reduces oropharyngeal deposition, thereby reducing systemic absorption of ICS.

Preliminary data suggest that adrenal suppression occurs only when inhaled doses of > 1,500 µg daily are used. More sensitive measurements of systemic effects include indices of bone metabolism (e.g. serum osteocalcin, urinary pyridinium crosslink excretion) and, in children, short-term growth of the lower leg, which can be increased at inhaled doses as low as 800 µg. The clinical relevance of these measurements is unclear. Nevertheless, it is important to reduce the risk of systemic effects by using the lowest dose of ICS needed to control asthma and by using a large-volume spacer to reduce oropharyngeal deposition.

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