



# Pharmacology of corticosteroids

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## Introduction

Glucocorticoids (GCs) are the most effective treatment of asthma. They have been used orally in asthma for more than 40 yr and by inhalation for over 20 yr. Although we do have this long experience with these compounds, many key issues concerning their proper place in the management of asthma still remain a matter of some uncertainty. The recognition of asthma as an inflammatory disease has led to a change in treatment strategy for this disease. Inhaled GCs for example have been the recommendation of recent major consensus panels with the goal being the prevention of asthma symptoms in patients with moderate and severe chronic asthma (Table 1) (1).

In this paper, we will analyse the available data on GC pharmacology in order to address some of the following questions. (1) What are the main clinical and biological targets of GC? (2) When and with which route to use GC in acute asthma? (3) What is the amount of GC required to induce a remission in acute and chronic asthma? (4) Does one GC provide major therapeutic advantage over others? (5) How should GC therapy be scheduled during the day to optimize the treatment? (6) How long should we use GCs in the treatment of both acute and chronic asthma? (7) Why are GCs orally needed in GC-dependent patients and how to manage these patients? (8) What is GC resistance? (8) Should every asthmatic be started on inhaled GC therapy? (9) What are the long-term beneficial deleterious effects of GC?

## General Principles of Corticosteroids in Asthma

### WHAT ARE THE MAIN CLINICAL AND BIOLOGICAL TARGETS OF GCs?

GCs are beneficial in controlling asthma symptoms, reducing asthma exacerbations and hospitalizations, minimizing  $\beta_2$ -agonist consumption, improving baseline FEV<sub>1</sub> and decreasing (but not completely normalizing) bronchial hyperresponsiveness. GCs block the late-phase reaction following allergen provocation. GCs act upstream to

multiple inflammatory pathways characterizing asthma and this may explain why they would be more effective than therapies that target at only a single mediator or cytokine level. Recent biopsy and bronchoalveolar lavage studies have given insights into their cellular mechanisms of action (2–8). These well-designed studies concerned mostly short-term and medium-term effects of GCs. Long-term effects remain very seldom examined. The most striking evidence of GC action in asthma is the reduction of the cellular inflammatory infiltrate, with no or little effect on the increased thickening of the basal membrane. The reduction of bronchoalveolar eosinophil, T-cell and mast cell numbers during GC treatment is mainly due to the inhibition of the synthesis of chemotactic and activating inflammatory mediators such as cytokines. Thus, Robinson *et al.* have (6) found that after 2 weeks of 0.6 mg kg<sup>-1</sup> of prednisolone in 18 patients that Th2 cells (expressing IL-4 and IL-5 mRNA) decreased. Laitinen *et al.* (3) have found that, after 16 weeks of inhaled budesonide, mast cell and eosinophil numbers decreased within the bronchi, although T-cell number remained unchanged in this study. Lundgren *et al.* (4) have shown in six severe asthmatics treated for 10 yr with daily 600–800  $\mu$ g budesonide that T-cells and plasma cells within the airways decreased dramatically, although the eosinophils may persist in some patients, as observed by Booth *et al.* (5) after 3 months of inhaled fluticasone. It is clear that GCs do not necessarily reverse all the abnormalities of asthma, and the subepithelial fibrosis in particular. The exact mechanisms of action of GCs in asthma are, however, unknown (2,7).

Although T cells and GC receptors are the best candidates for GC action, a role for other cell types and transcription factors cannot be ruled out. Thus, the basic mechanisms of GC actions include activation of the intracellular GC receptor followed by binding of the receptor to specific DNA sites in the nucleus to regulate transcription of target genes (Fig. 1). Abnormal GC receptor binding to the GCs and to their specific DNA responsive element has been found in the peripheral blood T cells of GC-resistant patients (7). More recently, it has been recognized that GC–GC receptor complex interacts with transcription factors such as NF $\kappa$ B and AP-1, and this is likely to be a major mechanism by which GCs inhibit the transcription of several pro-inflammatory cytokines and chemokines in asthma. The airway epithelium could also be an important site of action of topical GCs, as it expresses many cytokines such as GM-CSF, MCP-1 and

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TABLE 1. Classification of asthma severity adapted from the recent guidelines (1)

Asthma severity	Clinical features before treatment	Lung function	Regular medication required to maintain control
Intermittent	<ul style="list-style-type: none"> <li>● Brief symptoms &lt;1 time per week</li> <li>● Nocturnal asthma symptoms &lt;2 times per month</li> <li>● Asymptomatic between exacerbations</li> <li>● No limitation of everyday activities, no loss of work or schooling</li> </ul>	<ul style="list-style-type: none"> <li>● PEF and FEV<sub>1</sub> ≥ 80% predicted or personal best value at baseline</li> <li>● PEF variability* &lt;20%</li> </ul>	<ul style="list-style-type: none"> <li>● Occasional need for short-acting β<sub>2</sub>-agonists (less than 1 time per week)</li> </ul>
Mild persistent	<ul style="list-style-type: none"> <li>● Exacerbations &gt;1 time per week</li> <li>● Nocturnal asthma symptoms &gt;2 times per month</li> </ul>	<ul style="list-style-type: none"> <li>● PEF and FEV<sub>1</sub> ≥ 80% predicted or personal best value at baseline</li> <li>● PEF variability* 20–30%</li> </ul>	<ul style="list-style-type: none"> <li>● Inhaled daily GC (children begin with a trial of cromolyn)</li> <li>● Long-acting β<sub>2</sub>-agonists may be needed (particularly for nocturnal asthma)</li> <li>● Short-acting β<sub>2</sub>-agonists (as needed if sufficient); consider theophylline</li> </ul>
Moderate persistent	<ul style="list-style-type: none"> <li>● Exacerbations &gt;2 times per week</li> <li>● Nocturnal asthma symptoms &gt;1 time per week</li> <li>● Symptoms requiring β<sub>2</sub>-agonists almost daily</li> </ul>	<ul style="list-style-type: none"> <li>● PEF and FEV<sub>1</sub> 60–80% predicted or personal best value at baseline</li> <li>● PEF variability* &gt;30%</li> </ul>	<ul style="list-style-type: none"> <li>● Inhaled daily GC (children begin with a trial of cromolyn)</li> <li>● Long-acting β<sub>2</sub>-agonists may be needed (particularly for nocturnal asthma)</li> <li>● Short-acting β<sub>2</sub>-agonists (as needed if sufficient); consider theophylline</li> </ul>
Severe persistent	<ul style="list-style-type: none"> <li>● Frequent exacerbations</li> <li>● Frequent nocturnal asthma</li> <li>● Continuous symptoms</li> <li>● Physical activities limited</li> <li>● Hospitalization for asthma</li> </ul>	<ul style="list-style-type: none"> <li>● PEF and FEV<sub>1</sub> &lt;60% predicted or personal best value at baseline</li> <li>● PEF variability* &gt;30%</li> </ul>	<ul style="list-style-type: none"> <li>● Inhaled daily high dose of GC</li> <li>● Long-acting β<sub>2</sub>-agonists</li> <li>● Frequent use of oral GCs</li> <li>● Short-acting β<sub>2</sub>-agonists</li> <li>● Consider theophyllines</li> </ul>

Asthma severity may be clinically and functionally assessed over the previous 12 months by taking a careful history from the asthmatics (including frequency and severity of symptoms and their response to treatment) and by measuring airway obstruction by spirometry and ambulatory monitoring of PEF.

\*PEF variability = [(evening PEF – morning PEF)/(evening PEF + morning PEF)] × 1/2.

RANTES, in addition to GC receptors. Thus, topical steroids inhibit the expression of these cytokines in the airway epithelium. Increased AP-1 has been observed also in asthmatic epithelium (9). In acute severe asthma, other effects of GCs include inhibition of airway microvascular leakage and oedema and increased expression of β<sub>2</sub>-adrenergic receptors which may lead to increase efficacy of inhaled β<sub>2</sub>-agonists.

## Corticosteroids in Acute Severe Asthma

### WHEN, HOW MUCH AND WITH WHICH ROUTE TO USE GCs IN ACUTE ASTHMA?

In acute severe asthma, which does not respond to bronchodilators, GCs should be used early and systematically. This is known to shorten the course of asthma, to prevent

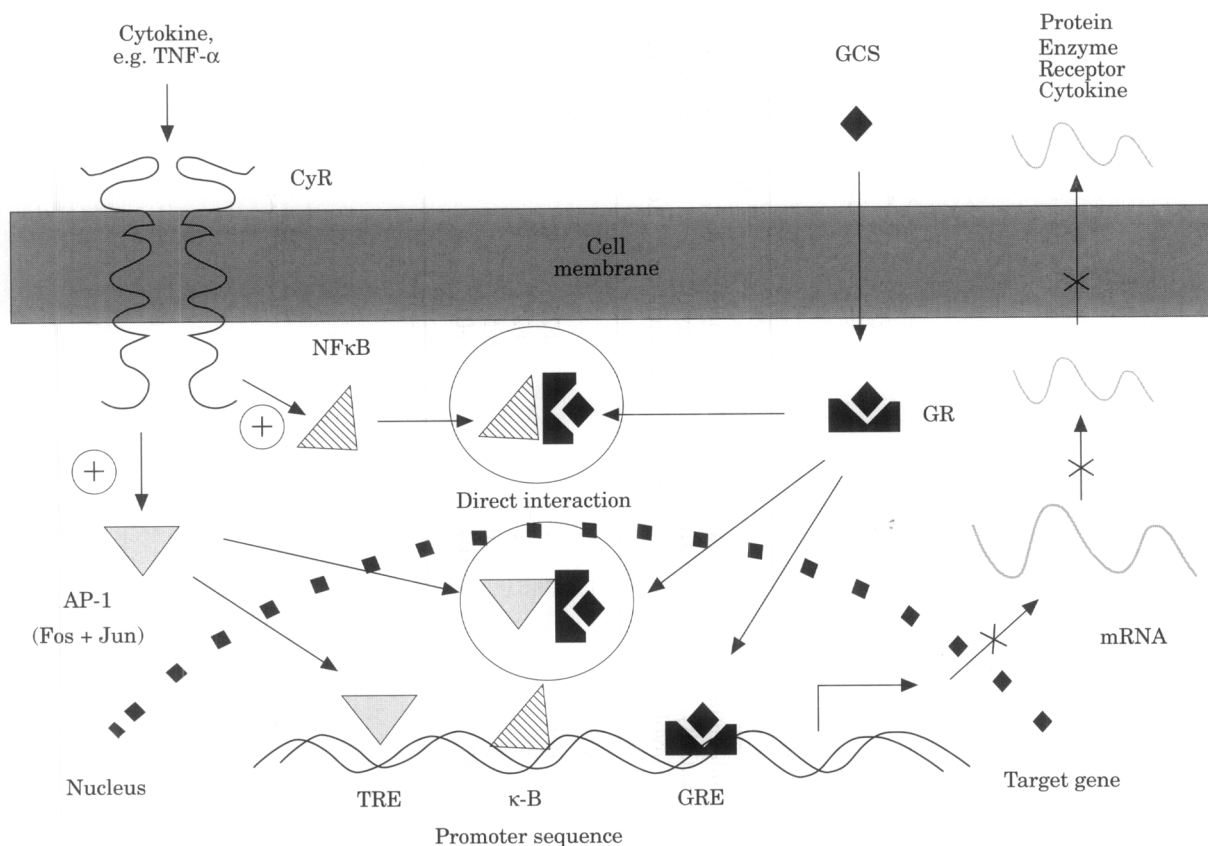


FIG. 1. Diagrammatic representation of the action of glucocorticoids (GCs) in inhibiting gene transcription of many proteins such as enzymes, receptors and cytokines in asthma. An increase in certain regulatory transcription factors such as activator protein-1 (AP-1) or nuclear factor  $\kappa$ B (NF $\kappa$ B) through cytokine-receptor activation [e.g. by tumour necrosis factor  $\alpha$  (TNF- $\alpha$ )] may occur in asthma. GCs penetrate into the cell and bind to glucocorticoid receptor (GR) which immediately translates to the nucleus to bind to glucocorticoid response elements (GRE). However, one of the main effects of the activated GR is to interact directly with transcription factors such as AP-1 and NF $\kappa$ B, thus preventing their binding to their DNA binding sites (e.g. TRE and  $\kappa$ -B respectively). This would in turn lead to a reduction or suppression of transcription of several protein genes. Many inducible cytokine genes do not have a regulatory GRE sequence on their promoter region and, therefore, the main effect of GCs would be to prevent binding of transcription factors to DNA. (Reproduced by permission of Dr I. Adcock.)

relapses and to reduce hospitalization rates, especially in patients with high risk of fatal asthma (10). In ambulatory patients, the optimal dose and schedule of administration have not been defined and controlled trials are needed. In adults, it is usual to administer orally 0.5–1 mg kg<sup>-1</sup> day<sup>-1</sup> of short-acting GCs (e.g. prednisolone) (10). Patients requiring hospitalization may require higher doses of GCs, although some investigators have not found any advantage from using high doses administered intravenously (e.g. 1 versus 6 mg kg<sup>-1</sup> day<sup>-1</sup> of IV methylprednisolone) (10,11). In one study, there was no apparent advantage of using intravenous hydrocortisone compared with oral prednisolone in acute severe asthmatic patients not in respiratory failure (12).

#### DOES ONE GC PROVIDE MAJOR THERAPEUTIC ADVANTAGE OVER OTHERS?

Most of the available GCs have been used in the treatment of acute severe asthma and there are no data suggesting

that one compound is better than another at comparable doses (10). There are, however, differences in side-effects and costs. Thus, methylprednisolone, because of its greater anti-inflammatory potency, its lower mineralocorticoid activity and its lower price by comparison with hydrocortisone, may be the drug of choice for intravenous therapy (10). Moreover, there is some evidence that methylprednisone is distributed better into the lungs than prednisone (13) and prednisolone (14) (Table 2). Concerning the use of prodrugs such as cortisone and prednisone, which need to be hydroxylated in the liver to become active, there is no evidence that, in the absence of liver disease, these compounds are any less effective than prednisolone or methylprednisolone, which are active *per se* (10). A high dose of intramuscular triamcinolone was found to be more effective than oral prednisone in terms of improved lung function, reduction in emergency room visits and hospitalizations, but steroid side-effects were greater with triamcinolone acetonide (15). However, optimal dosage and mode of administration need to be defined with triamcinolone.

TABLE 2. Pharmacokinetic parameters of the most common systemic GCs

	Plasma half-life (h)	Biological half-life (h)	Volume of distribution [l (1.73 m <sup>2</sup> ) <sup>-1</sup> ]	Clearance [ml min <sup>-1</sup> (1.73 m <sup>2</sup> ) <sup>-1</sup> ]	Anti-inflammatory activity (thymic involution)	Anti-inflammatory activity (anti-granuloma)	Mineralocorticoid activity (Na retention)	Relative affinity for lung tissue (with respect to dexamethasone)
Cortisol	1.9 ± 0.11	8-12	70	425.5	1	1	1	0.9
Prednisone	2.25 ± 1.25	12-36			0.9	1	0.25	
Prednisolone	3.25 ± 0.58	12-36	53.5 ± 13.5	198 ± 38	4	2.7	0.25	1.6
Methylprednisolone	2.58 ± 0.19	12-36	91.0 ± 9.9	384 ± 56.2	3	6	0.5	4.2
Dexamethasone	4.37 ± 1.16	36-54	33.4 ± 4.2	216 ± 21.5	47	104	<0.01	1

## HOW SHOULD GC THERAPY BE SCHEDULED DURING THE DAY AND FOR HOW LONG IN THE OPTIMIZATION OF THE TREATMENT IN ACUTE SEVERE ASTHMA?

Systemic GC should be continued at least until symptoms are controlled and pulmonary function is stably restored to the patient's normal or best value. Both overtreating and undertreating asthma may be harmful, because of either side-effects or relapse of uncontrolled asthma. In acute asthma, one would assume that overtreating is not a critical issue (because of the shortness of the GC course) although undertreating may lead to relapse of asthma attack. Clinicians may need markers to set the right level of treatment. However, such markers do not exist even if Skedinger *et al.* (16) have recently shown in nine patients experiencing an asthma exacerbation that the percentage of blood eosinophils, the serum and intracellular eosinophil cationic protein (ECP) decreased significantly after 7–9 days of oral prednisolone (starting with 30 mg daily). These markers did not correlate with each other or with clinical parameters. The results of this study should be compared with those of Wever *et al.* (17) who found in 20 symptomatic patients followed for 6 months and monitored once monthly (and during exacerbations) that there was a correlation between serum ECP and FEV<sub>1</sub>. Thus, duration of treatment and a tapering schedule are very common practice and must be individualized on the basis of the severity of the asthma exacerbation and the patient's previous history. After a short treatment course (1 week), GCs can be stopped abruptly as there is no evidence of hypothalamic–pituitary–adrenocortical suppression. Longer courses may require gradual dose reduction to allow adrenal recovery. On the other hand, gradual dose reduction is also necessary in more severe patients to avoid rebound asthma and other drugs (high-dose inhaled GCs in particular) may be used during this period.

## Oral Corticosteroids in Chronic Asthma

### GC-DEPENDENT ASTHMA: WHY AND HOW TO MANAGE?

Most asthmatic patients are well controlled by inhaled medications. Although GCs are usually given by inhalation, it is necessary to give them orally in some patients (so called GC-dependent asthmatics). This patient group is very heterogeneous, some being stable with a subnormal lung function and a GC dose requirement around 10 mg daily, others being unstable although they are taking high dose of GC every day (18). There is so far no apparent evidence that GC-dependent asthmatics bind, distribute or metabolize GC differently to asthmatics naive to GCs and normal subjects (2,7,10). Therefore, one does not need to assess GC pharmacokinetics in GC-dependent asthmatics. Again, as for acute severe asthma, there is no evidence that one compound is better than another at comparable doses. Although a twice-daily (8.00 a.m. and 4.00 p.m.) regimen

has the best anti-inflammatory effect, it is advised to give oral GCs once daily or every other day, in the morning (at 8.00 a.m.), in order to minimize suppression of the circadian rhythm of the hypothalamic–pituitary–adrenocortical system and to reduce the side-effects. Moreover, this regimen may improve compliance. In contrast, splitting the daily dose of GCs into several small administrations markedly increases the likelihood of adrenal suppression. The effectiveness of the alternate day regimen has not been established. As stated above, a high dose of intramuscular triamcinolone was found to be more effective than oral prednisone (15). However, because of greater steroid side-effects with triamcinolone this regimen is not recommended. The need for prolonged oral GCs should be documented by inadequate control despite maximal use of other treatment approaches (trigger factor control such as allergen avoidance, high dose of inhaled GC, long-acting  $\beta_2$ -agonists and theophyllines) and monitored by diary card and pulmonary function tests. A careful monitoring of the side-effects should also be performed, comprising a search for hypothalamic–pituitary–adrenal axis, bone density changes, abnormal glucose metabolism, hypertension, renal and ocular side-effects. There is no consensus as to how and how often should these tests be performed. GC sparing agents have been tried in such patients without any dramatic success (19). Trials of dose reduction must be constantly attempted. Inhaled GC is beneficial in trying to achieve the lowest dose of oral GC needed to control the disease (10). The inhaled dose to use is another area of uncertainty since 1500  $\mu\text{g}$  did not appear to be more effective than 300  $\mu\text{g}$  daily in these patients when symptoms and PEF rate were used as outcome parameters (20), but further studies are in progress.

### WHAT IS GC RESISTANCE?

Most patients with asthma respond well to GCs. However a handful of patients have little or no change in pulmonary function under a GC treatment and thus are classified as GC resistant. True GC-resistant asthmatics are rather rare (7). A poor response to GCs could be related to abnormal absorption, metabolism or a defect in cellular and molecular actions. As for corticoid dependence, there are no clear-cut data demonstrating a role for abnormal pharmacokinetics in corticoid resistance. For example, Schwartz *et al.* (21) and Kamada *et al.* (22) found a rapid GC clearance (mainly cortisol and prednisolone) in 4/4 adults with GC resistance and 13/22 children with poorly controlled asthma respectively, although Corrigan *et al.* (23) and Lane *et al.* (24) did not. The molecular mechanisms may be related to an abnormal GC receptor binding to either its ligand (e.g. GC) or its target (e.g. DNA), the latter being due to an excessive expression of the transcription factor AP-1. Further studies are in progress in this particular group because the mechanism involved here may give insights into what is happening in GC-dependent asthmatics and maybe in asthmatics in general. It is not known whether there is any down-regulation of GC receptor in the airways with treatment with topical GCs.

## SHOULD EVERY ASTHMATIC BE STARTED ON INHALED GC THERAPY?

The issue of whether inhaled GC should be introduced for patients with very mild asymptomatic asthma is still a matter of debate. This question and the two following ones raise the same concern about the monitoring of asthma inflammation. Again, overtreatment and undertreatment asthma may be harmful and markers are needed to give a measure of this inflammation. Increasing evidence suggest that even in mild asthmatics the airways show evidence of inflammation (8,25,26). There is a wide range of pathological abnormalities and a wide variability among patients. Although overall correlations are found between these abnormalities and clinical parameters of asthma severity and activity, there is a lack of accurate clinically useful tools that clearly indicate this fact (27). For example, Wang *et al.* (8) have recently demonstrated in 23 mild asthmatics that 4 months of beclomethasone dipropionate (BDP) 500  $\mu\text{g}$  twice daily led to a significant decrease in endobronchial inflammatory markers (GM-CSF, IL-8 and EG2 staining) although (only) 7/12 BDP-treated patients (versus 0/11 placebo-treated patients) became free of symptoms. Do the five mild patients who did not improve clinically under BDP treatment need to carry on their inhaled GC treatment (maybe at higher dose) and what are the data in the literature helping us to convince the seven patients who did clinically improve to carry on their inhaled GC treatment? Would 2 mg BDP daily be better than this 1 mg daily treatment dose? How should we modulate this regimen? The usefulness of the blood measurement of ECP has mainly been assessed in cross-sectional studies showing its relation to asthma severity as measured by FEV<sub>1</sub> and histamine PC<sub>20</sub> (27) and to asthma activity as measured by peak expiratory flow (PEF) diurnal variations (17). Elevated levels of blood ECP seem to identify patients at risk of inflammatory exacerbations, maybe representing those not optimally treated with inhaled GCs. We need more longitudinal studies addressing specifically this question. Recently, nitric oxide in exhaled air has been used as a non-invasive inflammatory marker of asthma severity (28) and its level is inhibited by inhaled GC therapy (29). Measurements of inflammatory markers in induced sputum are also being evaluated in this regard (30).

Selroos *et al.* (31) have recently tried to address the question of early versus late introduction of inhaled GCs by following during 2 yr 105 consecutive patients with mild or moderate asthma not previously treated with inhaled GCs. They were using inhaled bronchodilators of three or more doses per week and/or they were experiencing symptoms during day or night and/or they had PEF or FEV<sub>1</sub> values less than 75% of predicted normal values. They were divided into six groups depending on the duration of symptoms (<6 months, 6–12 months, 1–2 yr, 2–5 yr, 5–10 yr and >10 yr). They were all given budesonide for 2 yr (800  $\mu\text{g}$  daily for most of them) in an open trial. Efficacy was evaluated at 3 months, 1 yr and 2 yr by measuring FEV<sub>1</sub> and PEF. The group with asthma symptoms that lasted for less than 6 months had the greatest improvement in FEV<sub>1</sub> (+24%). Subjects with

asthma duration greater than 10 yr when treated with inhaled GC for the first time showed a worsening at the end of the 2-yr. A previous double-blind randomized parallel 2 yr study had shown that, when used as regular first-line treatment in patients with mild to moderate newly detected asthma, budesonide (600  $\mu\text{g}$  twice daily) was significantly more effective than inhaled terbutaline (32). Terbutaline-treated patients received budesonide (600  $\mu\text{g}$  twice daily) for the third year. Significantly poorer clinical improvement was seen by comparison with budesonide from the outset (33). In a study which followed 278 children with mild to moderate asthma treated for 3–6 yr with budesonide, Agertoft and Pedersen (34) found that children who started inhaled GC early (e.g. within 2 yr after asthma was diagnosed) had a faster and a greater lung function improvement than others. In addition, the accumulated dose of inhaled GCs taken by the former after 4.5 yr of continuous treatment was significantly lower than the dose taken by the group of children in whom budesonide was not initiated until after more than 5 yr of continuous symptoms. These results both in adults and in children provide evidence that early treatment of symptomatic asthmatics with inhaled GCs may prevent the development of chronic airflow obstruction and the rapid decline in FEV<sub>1</sub> of some asthmatics. However, the benefits of prescribing inhaled GCs at the first diagnosis of asthma to all patients would require evaluation in a large international placebo-controlled trial.

## WHAT IS THE AMOUNT OF INHALED GC REQUIRED AND FOR HOW LONG?

The question of how much and for how long inhaled GCs should be used for the mild asthmatics will not be answered before we identify markers of airway inflammation that correlate with progression of asthma. The use of 2 mg daily of BDP leads to a better control of asthma symptoms than lower doses. It is worth mentioning that the clinical dose-response relationship is a rather shallow one such that, for example, there was not much difference in effect on bronchial responsiveness between 400 and 800  $\mu\text{g}$  daily of budesonide. Boe *et al.* (35) did not find any statistically significant differences between the effect of daily doses of 400–800  $\mu\text{g}$  daily of budesonide or between 400 and 1000  $\mu\text{g}$  daily of BDP on PEF and diary recordings. Dale *et al.* (36) found very similar results using 100–800  $\mu\text{g}$  daily of fluticasone propionate in 672 patients. No formal dose-response studies have been performed in pre-school children, so that the optimal dose in this age group is not known. In school children, 200–800  $\mu\text{g}$  daily from a spacer and 1000–2000  $\mu\text{g}$  daily of budesonide from a nebulizer have been shown to be roughly equivalent (37,38). Furthermore, there is no published evidence that increasing the dose above 2 mg daily in adults increases the beneficial response (39). It is advocated that starting with a relatively high dose of inhaled GC first to gain rapid control of the asthma is a better policy with the dose reduced gradually to a minimum afterwards. When asthma worsens, the dose of GC can be temporarily doubled until control is

re-established although there is no good evidence so far to indicate the efficacy of this approach. How long a patient should remain on GC therapy once the disease is controlled is not known. However, it is clear that, on discontinuing treatment, asthmatics do worsen after a variable period of time.

One issue that is discussed a lot is that of the potential systemic dose-dependent side-effects of long-term treatment, particularly the potential for blocking the hypothalamic–pituitary–adrenal axis and inducing osteoporosis. Our experience with inhaled GCs so far is that these problems are unlikely to be of clinical importance although, in some susceptible patients, clinically significant side-effects may be a problem. For patients for whom currently available inhaled GCs are incompletely effective prolonged oral GCs should be considered with the limitations described above. Use of other anti-asthmatic drugs should also be considered. The combination of inhaled GC with long-acting  $\beta_2$ -agonists indicates that doubling the dose of GC does not provide any benefit while the addition of a long-acting  $\beta_2$ -agonist to a low-dose GC treatment has additive effects. Other agents that may be worth considering in combination with low-dose GC include theophylline, particularly at low dose. Such a combination may be more important for patients needing high-dose GC for asthma control or for patients with poorly controlled asthma even when using high-dose inhaled GCs. Recently, Busse *et al.* (40) have shown that azelastine 6 mg twice daily was able to reduce significantly the daily inhalations of GC in a 12 week double-blind trial, without deterioration of lung function.

#### DOES ONE INHALED GC PROVIDE MAJOR THERAPEUTIC ADVANTAGE OVER OTHERS?

Inhaled GCs have different affinities for their cellular receptor and variable pharmacokinetic parameters (Table 3). The search for even more potent GCs than the ones currently available now continues. One wonders who much further breakthrough there will be as it appears difficult to devise a molecule that would be very active and not absorbed from the airway submucosa where the GC has to get to in order to effect its beneficial actions. In addition, it is not known whether a more potent GC would provide improved benefits given the shallow dose–response relationship of current GC at moderate and high dosages.

#### HOW SHOULD INHALED GC THERAPY BE SCHEDULED DURING THE DAY TO OPTIMIZE THE TREATMENT?

Initially, inhaled GC was given four times per day. It has since been shown that twice-daily regimens may be as effective as four times daily ones (41), but even this issue is the subject of controversy. Thus, Malo *et al.* (42) have recently demonstrated in a randomized parallel 6–12 months study that administering inhaled budesonide with a

Turbuhaler<sup>®</sup> device four times per day resulted in fewer ‘flare-ups’ in spite of less compliance and more frequent local side-effects than on a twice-daily regimen basis at daily doses of 800 and 1200  $\mu\text{g}$ . In order to improve compliance, once-daily regimens have been tested with conflicting results in a relatively short duration of follow-up (3–4 weeks). In a 12 month follow-up, double-blind, randomized study, Weiner *et al.* (43) have recently found in 40 moderate asthmatic patients that 400  $\mu\text{g}$  of budesonide twice daily (morning and bedtime) is more effective than a single dose of 800  $\mu\text{g}$  at bedtime (in terms of number of  $\beta_2$ -agonist inhalations, PEF variability and asthma symptom scores).

#### WHAT ARE THE PHARMACOKINETIC DATA AVAILABLE?

Pharmacokinetic data after inhalation are limited and can hardly be used as a criteria for selection of therapy. Concerning budesonide with a Turbuhaler<sup>®</sup>, for example, it has been shown in ten healthy volunteers using radio-labelled particles that lung deposition varies from  $14.8 \pm 3.3\%$  to  $27.7 \pm 9.5\%$  according to the inhalation flow (from a slow flow of  $36 \text{ l min}^{-1}$  to a normal flow of  $58 \text{ l min}^{-1}$  respectively (44). Concentrations in blood plasma are 1/8th of that in lung tissue (45). GCs are mostly active locally, as shown by Toogood *et al.* (46). Absorption of the swallowed fraction is usually largely metabolized to inactive metabolites in the liver (first-pass metabolism). Thus, the degree of first-pass metabolism and the amount absorbed from the airways (which is in turn dependent on the delivery system used and the efficacy with which it is used) determine to a large extent the potential for systemic side-effects. Mouth rinsing employed after using a spray reduces gut availability and obviates local adverse effects. When high doses are required for asthma control, the GC with the lowest bioavailability should be chosen (Table 3). One issue that is unclear is whether there is any development of ‘tachyphylaxis’ to the actions of GCs by GC-induced receptor downregulation or other mechanisms.

#### WHAT IS THE COST-EFFECTIVENESS OF INHALED GCs?

Long-term use of inhaled GCs has been shown to reduce inpatient hospital admissions and cost of care [in 36 budesonide-treated patients followed during 5 yr (47)]. In a 2.5 yr randomized controlled study in 274 patients, Rutten-van Möllen *et al.* (48) concluded that the addition of an inhaled GC to a  $\beta_2$ -agonist leads to significant benefits in FEV<sub>1</sub>, PC<sub>20</sub>, restricted activity days and symptom-free days with relatively low additional health care costs (\$201 per patient per year). Inhaled GCs have also been found to be cost-effective in pre-school (49) and school (34) children. Using budesonide to treat symptomatic children with asthma, aged 1–3 years, increased symptom-free days compared with placebo and reduced overall costs by \$9.5 per symptom-free day gained (50).

TABLE 3. Pharmacokinetic parameters of the most common inhaled GCs

	Plasma half-life (h)	Volume of distribution [(1.73 m <sup>2</sup> ) <sup>-1</sup> ]*	Clearance [l min <sup>-1</sup> (1.73 m <sup>2</sup> ) <sup>-1</sup> ]	Anti-inflammatory activity (thymic involution)	Relative skin blanching potency (with respect to dexamethasone)†	Relative affinity for lung tissue (with respect to dexamethasone)	Human lung GR complex half-life (h)	Systemic bioavailability (%)	
								Inhaled	Oral
Beclomethasone dipropionate	1.5			3.5	600	0.4		20	<20
Triamcinolone acetonide	1.5	100	0.8	5.3	330	3.6	3.9	21	22
Flunisolide	1.6	125	1	12.8	330	1.8	3.5		21
Budesonide	2.8	300	1.4	1	1980	9.4	5.1	25	11
Fluticasone	3.1	260	0.9		1200	18.0	10.5	20	<1

\*Increases with the lipophilicity of the drug.

†Correlates well with the GC receptor binding affinity.



## Conclusion

Thus GCs are the best medicines available at present to improve the clinical status and many of the underlying physiological abnormalities of most asthmatics. The relative safety of topical (inhaled) formulations has led to recommendations that GCs may be used more aggressively than in the past, as early as possible and for as long as possible in symptomatic asthmatics, with the goal of controlling asthma symptoms. There may be long-term beneficial effects. In the guidelines, a frequency of  $\beta_2$ -agonist use of more than three times per week is an indication for initiating inhaled GC therapy. There are, however, very few studies evaluating the outcome of these recommendations. In this paper the available data on GC pharmacology have been analysed and crucial unresolved issues have been highlighted. The asthmatic patient often has a distrust of GC therapy and the process of convincing the patient of the benefits of GC therapy is part and parcel of the management of the asthmatic, as is demonstrating to the patient the correct use of his or her inhaler since around 50% of our patients are either non-compliant or misusers (49).

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