REVIEW ARTICLE

# Inhaled Corticosteroids in the Treatment of Asthma Exacerbations: Essential Concepts

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**The use of systemic corticosteroids reduces hospitalizations in patients suffering an asthma attack and improves lung function within 6 to 12 hours of administration. However, despite the considerable body of positive evidence published in the last decade, doubts remain in regard to the effectiveness of inhaled corticosteroids. Analysis of this evidence has been cursory; crucial data on the mechanism of action of corticosteroids have been overlooked and there has been a failure to distinguish between antiinflammatory effects and so-called nongenomic effects. This review considers the biological basis for the effects of inhaled corticosteroids and analyzes the best data available on the use and therapeutic implications of inhaled corticosteroids for the treatment of asthma exacerbations.**

**Key words:** *Corticosteroids. Fluticasone. Budesonide. Beclomethasone. Acute asthma.*

## Conceptos básicos sobre la utilización de corticoides inhalados en el tratamiento de la exacerbación asmática

**El uso de corticoides sistémicos reduce las hospitalizaciones y mejora la función pulmonar al cabo de 6 a 12 h desde su administración en pacientes con crisis asmáticas. Sin embargo, a pesar de la considerable evidencia surgida de publicaciones durante la última década, los corticoides inhalados no se han considerado efectivos. El análisis de esta evidencia ha sido superficial, ya que se han obviado aspectos fundamentales relacionados con los mecanismos de acción y no se han distinguido los efectos antiinflamatorios de los denominados efectos no genómicos. Así pues, el objetivo de esta revisión es aclarar las bases biológicas de los efectos de los corticoides inhalados, analizar la mejor evidencia disponible con respecto a su uso en el tratamiento de las exacerbaciones asmáticas y las repercusiones terapéuticas que surgen de ella.**

**Palabras clave:** *Corticoides. Fluticasona. Budesonida. Beclometasona. Asma aguda.*

## Introduction

Asthma is a chronic disease characterized by hyperreactivity, reversible airflow limitation, and respiratory symptoms.[1] Asthma patients may experience exacerbations or crises, the intensity of which range from mild episodes–which may even go unnoticed by the patient–to extremely serious episodes that place a patient's life at risk and may even result in death (fatal or near-fatal asthma).[2] The most relevant factor when deciding treatment, consequently, is the severity of an asthma crisis. The main aims of treatment are to maintain adequate oxygen saturation using oxygen therapy, reduce airway obstruction by repeated use of bronchodilators (fast-acting $\beta$-agonists and anticholinergics), and finally, control of airway inflammation and prevention of relapses by means of the administration of systemic corticosteroids.[3] The evidence indicates that the use of oral or parenteral corticosteroids reduces hospitalizations and improves

lung function; that said, these drugs are slow to take effect (6 to 12 hours)[4,5] because they depend on complex cellular mechanisms. A study by Husby et al,[6] published almost 15 years ago, was an important landmark in regard to the use of inhaled corticosteroids in the treatment of severe airway diseases. This randomized, controlled trial, which compared the administration of a single dose of 2 mg of inhaled budesonide or a placebo to children hospitalized for severe croup, reported rapid clinical improvement (within 2 hours of treatment) in patients administered budesonide. A number of subsequent pediatric studies evaluated the effects of inhaled corticosteroids in the treatment of asthma exacerbations. These also demonstrated early effects on lung function and clinical variables,[7,8] which did not seem to be attributable to the action of systemic corticosteroids. Despite the substantial positive evidence provided by publications in the last decade, however, inhaled corticosteroids have not been considered effective in treating asthma exacerbations. Nonetheless, analysis of the evidence has been cursory, as certain fundamental aspects of the mechanisms of action of these drugs have been overlooked. An adequate distinction has failed to be drawn, for example, between the classical anti-inflammatory

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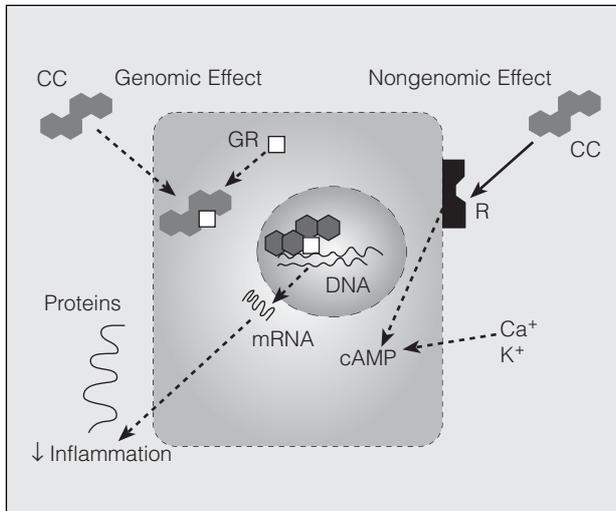E-mail: gurodrig@adinet.com.uy

**Figure 1. Corticosteroid (CC) action mechanisms. In the anti-inflammatory (or genomic) effect, depicted on the left of the diagram, a CC molecule enters the cell cytoplasm and binds with a glucocorticoid receptor (GR). The complex then diffuses within the cell nucleus, binds to specific DNA sequences, and increases the synthesis of messenger RNA (mRNA) and new protein molecules. Nongenomic effects, depicted on the right of the diagram, are the result of the CC molecule binding to a receptor (R) on the cell surface. This receptor then increases the value of second messengers–such as cyclic adenosinmonophosphate (cAMP)–which, in turn, increase the cell permeability of a number of ions.**

effects of these drugs and the effects referred to as nongenomic. Nor has course over time or its relationship with dosage been studied. Although a number of systematic and nonsystematic reviews have professedly analyzed the effects of inhaled corticosteroids on severe asthma, [9-11] their conclusions cannot be considered valid given that they generally included different types of studies, with dosages and time frames that were not comparable; in one such review, for example, a combined analysis was made of a series of studies in which hospital stays lasted between 2 and 12 hours.[9] The aim of this particular review, therefore, is to clarify the nature of the biological bases for the effects of inhaled corticosteroids and to analyze, in accordance with pre-established criteria, the best evidence available with respect to their use in treating asthma exacerbations.

## Biological Bases for the Effects of Corticosteroids

Corticosteroid mechanisms of action on the inflammatory process are complex. On the one hand there is the classical anti-inflammatory action, in which corticosteroid molecules are diffused across the target cell membrane and bind with corticosteroid receptors (proteins) in the cytoplasm (Figure 1).[12] The corticosteroid-receptor complex is then rapidly transported to the cell nucleus, where it binds to specific DNA sequences and changes the gene transcription mechanism so that messenger RNA molecule synthesis is activated, leading to the production of new proteins. Corticosteroids reduce

inflammation, therefore, by increasing the synthesis of anti-inflammatory proteins. As the cell genome is involved in this mechanism, this anti-inflammatory effect is alternatively referred to as a genomic effect. In terms of response, after the corticosteroid molecule enters the cell, hours or even days may elapse before significant quantities of new proteins are produced. This explains the 6 to 12 hours' delay (demonstrated by clinical trials[4,5]) in detecting the beneficial action of systemic corticosteroids.

More recently, however, it has been demonstrated that the corticosteroids have biological effects that are independent of the gene transcription process.[13,14] Although most of the research on this nongenomic effect has been performed in the last 10 years, the first evidence of this alternative response was reported as early as 1942 by Selye,[15] who observed that certain corticosteroids had an anesthetic effect within minutes of administration. The acute cardiovascular effects of aldosterone, which become evident as early as 5 minutes following administration, were described 20 years later.[16] The nongenomic effects of corticosteroids, which function by generating cyclic adenosinmonophosphate or protein kinases as a second set of messengers, produce a much faster response–within seconds or minutes–that is mediated by receptors located in the cell membrane.

More recent research has centered on the nongenomic effects of inhaled corticosteroids on the airways, most particularly on mucosal blood flow in both asthmatic and healthy subjects.[17,18] These studies show that there is a significant increase in mucosal blood flow in asthmatic patients compared to healthy subjects, and that inhaled fluticasone has the effect of reducing flow by causing vasoconstriction.[19] The reduction is transient, however, reaching a peak 30 minutes after administration of the corticosteroid and returning to baseline values after 90 minutes (Figure 2). Flow reduction is affected by the dose administered (with larger doses leading to greater reductions), and by baseline flow values (with greater baseline values leading to greater reductions). Finally, the vasoconstrictor effect is not specific to fluticasone but is also produced by other inhaled corticosteroids such as beclomethasone and budesonide; fluticasone and budesonide are both more potent than beclomethasone, however.

Blood flow reduction in the airway mucosa is a consequence of the corticosteroid vasoconstrictive effect on the smooth muscle of mucosal vessels. Figure 3 shows how the sympathetic nerve endings that form synapses with smooth muscle cells release norepinephrine to the synaptic space, where it binds to the $\alpha$-receptors of the muscle cells, causing the muscles to contract. There are a number of mechanisms that control the quantity of norepinephrine released to the synaptic space and, consequently, the extent of receptor stimulation. In one mechanism, some of the neurotransmitter molecules are taken back up into the presynaptic nerve terminal so that they can be reused at a later stage. In a second mechanism, norepinephrine is

taken up in the muscular postsynaptic endings, where it is metabolized by intracellular enzymes such as monoaminoxidase and catechol-O-methyltransferase. Corticosteroids inhibit the second of these norepinephrine uptake mechanisms, by allowing neurotransmitters to accumulate in the synaptic space and stimulate the $\alpha$-receptors. This in turn, leads to vasoconstriction.

To sum up, corticosteroids have a dual effect on asthmatic patients (Table 1). In particular, the nongenomic effect occurs within minutes, is transient, is dose-dependent, and is proportional to the initial hyperperfusion level. These fundamental features of corticosteroid use should be taken into account when administering inhaled corticosteroids to patients with severe asthma. Inhaled corticosteroids should, essentially, be administered frequently and in high doses in order to maintain the effect, most particularly in patients with severe obstruction.

## The Evidence

With a view to identifying studies of inhaled corticosteroids used to treat asthma exacerbations, 3 strategies were applied to the literature search. First, the MEDLINE, EMBASE, and CINAHL databases were consulted–for literature up to and including December 2005–using the following medical subject headings as search terms: *corticosteroids* OR *dexamethasone* OR *fluticasone* OR *beclomethasone* OR *budesonide* OR *flunisolide* AND *acute asthma* OR *status asthmaticus*. Second, the same terms were used to consult the Cochrane Central Register of Controlled Trials (4th edition, 2005). Finally, the search was completed with the references listed in the studies identified above and in reviews published on the subject. Only full-length studies were considered, i.e., all studies in abstract form were excluded. Studies were screened according to the following specific selection criteria: *a)* randomized controlled studies performed by emergency or casualty
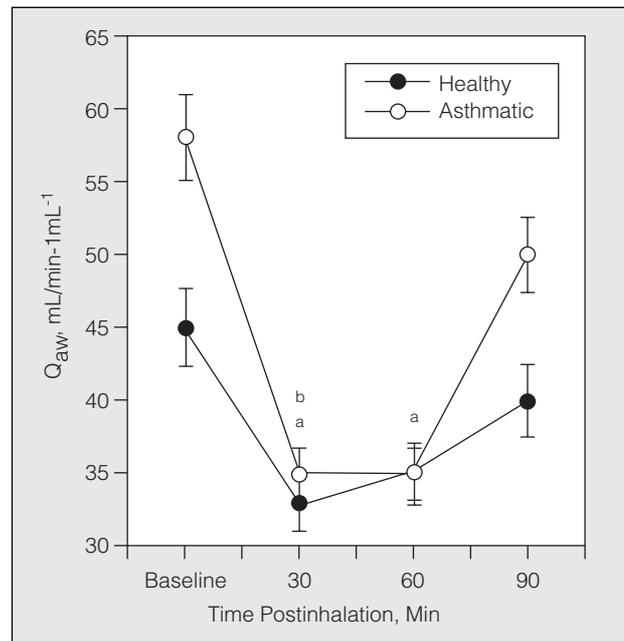


Figure 2. Effect produced by 880 µg of inhaled fluticasone on airway mucosal blood flow ($Q_{aw}$) in 10 asthmatic subjects and 10 healthy subjects (mean±SE). [a]Healthy subjects: *P*=.01 in relation to baseline. [b]Asthmatic subjects: *P*=.01 in relation to baseline. (Source: Adapted from Kumar et al.[17])

TABLE 1
**Corticosteroid Effects on Airway Inflammation**[14]

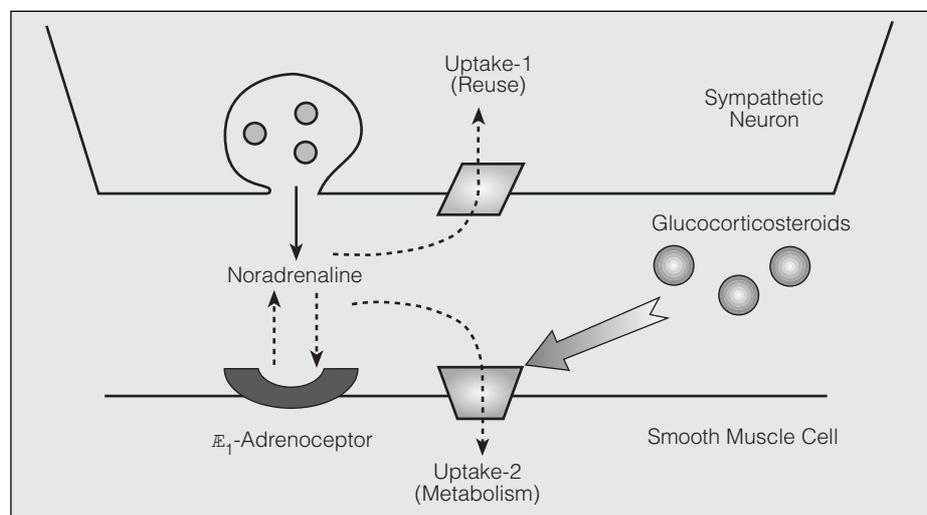|  | **Genomic Effects** | **Nongenomic Effects** |
|---|---|---|
| Action | Regulation of proinflammatory gene transcription | Catecholamine reuptake inhibition |
| Onset | Slow (hours or days) | Rapid (minutes) |
| Target | Angiogenesis, hyperperfusion, hyperpermeability, leukocyte recruitment | Hyperperfusion |



**Figure 3. Acute corticosteroid effects produced on the smooth muscle cell in airway mucosal blood vessels. (Source: Adapted from Wanner et al.[14])**

TABLE 2
**Characteristics of the Randomized, Double-Blind, Placebo-Controlled
Studies Reviewed**[*]

| Study | Population | Protocol | Results |
|---|---|---|---|
| Pansegrouw[7] | 40 adults (aged 18-70 y) $FEV_1$<70% | FEN 400 µg + BEC 200 µg in MDI×1 vs FEN 400 µg + PL | $FEV_1$ at 60 min: BEC>PL |
| Rodrigo & Rodrigo[20] | 94 adults (aged 18-50 y) $FEV_1$<50% | SAL 400 µg + FLU 1 mg MDI every 10 min for 3 h vs SAL 400 µg + PL every 10 min for 3 h | PEF, $FEV_1$, Clinical index at 120, 150, 180 min: FLU>PL Hospitalization 180 min: FLU>PL |
| Afilalo et al[21] | 4 adults (aged >18 y) $FEV_1$ 40%-59% | SAL 2.5 mg nebulization×1 + BEC 1 mg MDI (0.30 min, 1, 2, 4 h) vs SAL 2.5 mg nebulization×1 + PL | PEF, $FEV_1$ at 60, 120, 240 min: BEC=PL Hospitalization 6 h: BEC=PL |
| Singhi et al[22] | 60 children (aged 3-13 y) PEF 50%-70% | SAL 0.15 mg/kg nebulization + BUD 400 µg MDI every 30 min×3 vs SAL 0.15 mg/kg nebulization + PL | PEF, RF, Clinical index, $RO_2$ at 120 min: BUD>PL. Corticosteroid use, Hospitalization 4 h: BUD>PL |
| Tsai et al[23] | 24 children (aged 6-17 y) PEF 100 L/min | TE 0.1 mg/kg nebulization every 6 h×2 + BUD 0.05 mg/kg nebulization×1 vs TE 0.1 mg/kg nebulization every 6 h×2 + PL | PEF, Clinical index at 60, 180 min: BUD=PL |
| Rodrigo & Rodrigo[24] | 116 adults (aged 18-50 y) $FEV_1$< 50% | SAL 400 µg + IB 84 µg MDI every 10 min for 3 h + FLU 1 mg MDI every 10 min for 3 h vs SAL 400 µg + IB 84 µg MDI every 10 min for 3 h + PL | PEF, $FEV_1$ at 120, 180 min: FLU>PL. Hospitalization 3 h: FLU>PL |
| Estrada-Reyes et al[25] | 116 adults (aged 18-50 y) $FEV_1$<50% | SAL 400 µg + IB 84 µg MDI every 10 min for 3 h + FLU 1 mg MDI every 10 min for 3 h vs SAL 400 µg + IB 84 µg MDI every 10 min for 3 h + PL | PEF, $FEV_1$ at 120, 180 min: FLU>PL. Hospitalization 3 h: FLU>PL |
| Sekerel et al[26] | 67 children (aged 6-15 y) $FEV_1$ 70%-90% | SAL 0.15 µg/kg nebulization every 60 min×3 + BUD 1 mg nebulization every 60 min×3 vs SAL 0.15 mg/kg every 60 min×3 + PL | $FEV_1$ at 210 min: BUD=PL |
| Sung et al[27] | 44 children (aged 6 months-18 y), clinical index: moderate-severe | PRED 1 mg/kg PO×1 + SAL 0.15 mg/kg nebulization every 30 min×3 + BUD 2 mg nebulization×1 vs PRED 1 mg/kg PO×1 + SAL 0.15 mg/kg nebulization every 30 min×3 + PL | Clinical index at 180 min: BUD=PL |
| Guttman et al[28] | 60 adults $FEV_1$<40% | SAL 2.5 mg nebulization 0, 0.5, 1, 2, 4, 6, 8, 10 h + MET 80 mg IV every 6 h×2 + BEC 1 mg MDI 0, 0.5, 1, 2, 4, 6, 8, 10 h vs SAL 2.5 mg nebulization 0, 0.5, 1, 2, 4, 6, 8, 10 h + MET 80 mg IV every 6 h×2 + PL | PEF, $FEV_1$ at 60, 120, 240 min: BEC=PL. Hospitalization 12 h: BEC=PL |
| Nuhoglu et al[29] | 26 children (aged 5-15 y) clinical index: moderate | SAL 0.15 mg/kg nebulization×3 + MET 1 mg/kg IM + BUD 1 mg nebulization×1 vs SAL 0.15 mg/kg nebulization×3 + MET 1 mg/kg IM + PL | Clinical index at 60 min: BUD=PL. PEF at 60 min: BUD>PL |
| Scarfone et al[8] | 105 children (aged 1-17 y) clinical index: moderate | SAL 0.15 µg/kg nebulization every 30 min×3 + DE 1.5 mg/kg nebulization every 30 min ×3 vs SAL 0.15 mg/kg nebulization every 30 min×3 + PRED 2 mg/kg PO | Discharge after 2 h: DE>PRED. Hospitalization 6 h: DE=PRED |
| Volovitz et al[30] | 22 children (aged 6-16 y), PEF 35%-75% | TE 5 mg nebulization×1 + BUD 1.6 mg TUR×1 vs TE 5 mg nebulization×1 + PREDN 2 mg/kg PO | PEF, clinical index at 60, 120, 180 min: BUD=PREDN |

*(Continued overleaf)*

TABLE 2
**Characteristics of the Randomized, Double-Blind, Placebo-Controlled
Studies Reviewed** (Continued)[*]

| Study | Population | Protocol | Results |
|---|---|---|---|
| Devidayal et al[31] | 80 children (aged 2-12 y) PEF 63% | SAL 0.15 µg/kg nebulization every 30 min×3+BUD µg/kg nebulization every 30 min×3 vs SAL 0.15 mg/kg nebulization every 30 min×3+PREDN 2 mg/kg PO | $SaO_2$, RF, clinical index, discharge at 120 min: BUD>PREDN |
| Schuh et al[32] | 101 children (aged 5-18 y) $FEV_1$<60% | SAL 0.15 mg/kg nebulization every 20 min×6+FLUT 2 mg/kg MDI×1 vs SAL 0.15 mg/kg nebulization every 20 min×6+PRED 2 mg/kg PO | $FEV_1$, FVC, Hospitalization 4 h: FLUT<PRED |
| Milani et al[33] | 34 children (aged 2-7 y) clinical index: moderate-severe | SAL 0.15 mg/kg nebulization+BUD 2 mg nebulization×1 vs SAL 0.15 mg/kg nebulization+PRED 1 mg/kg PO | Clinical index, $SaO_2$ at 60, 120, 240 min: BUD=PRED |
| Rodrigo[34] | 106 adults (aged 18-50 y) $FEV_1$<50% | SAL 400 µg+IB 84 µg MDI every 10 min for 3 h+FLUT 500 µg every 10 min for 3 h vs SAL 400 µg+IB 84 µg MDI every 10 min for 3 h+HYD 500 mg IV | PEF, $FEV_1$ at 150, 120, 180 min: FLUT>HYD. Hospitalization 180 min: FLUT>HYD |

[*]BEC indicates beclomethasone; BUD, budesonide; DE, dexamethasone; FEN, fenoterol; $FEV_1$, forced expiratory volume in 1 second; FLU, flunisolide; FLUT, fluticasone; FVC, forced vital capacity; HYD, hydrocortisone; IB, ipratropium bromide; IM, intramuscular route; IV, intravenous route; MDI, metered-dose inhaler; MET, methylprednisolone; PEF, peak expiratory flow; PL, placebo; PO, oral administration; PRED, prednisone; PREDN, prednisolone; RF, respiratory frequency; $RO_2$, oxygen requirement; SAL, salbutamol; $SaO_2$, arterial oxygen saturation; TE, terbutaline; TUR, Turbuhaler®.

departments, published in any language, and excluding studies on hospitalized patients; *b)* studies of children and adolescents (aged 18 months to 17 years) and of adults (aged 18 years and older) with asthma exacerbations satisfying the Global Strategy for Asthma Management and Prevention[1]; *c)* studies with subjects randomized to receive a single dose or multiple doses of an inhaled corticosteroid in addition to other medication such as *β*-agonists, anticholinergics, aminophylline, or systemic corticosteroids; and *d)* studies evaluating variables such as lung function, clinical indices, and hospitalizations, as also other physiological variables and adverse effects. Study variables were required to have been measured between 1 and 4 hours following commencement of the treatment protocol. In other words, in accordance with the arguments presented in the previous section, studies more than 4 hours after start of the treatment protocol, in order to avoid alterations caused by genomic or classical anti-inflammatory effects were excluded.

A total of 17 randomized, double-blind, placebo-controlled trials were identified in the literature search. Eight compared the use of an inhaled corticosteroid to placebo,[7,20-26] 3 an inhaled corticosteroid plus systemic corticosteroid to a systemic corticosteroid,[27-29] and the remaining 6 an inhaled corticosteroid to a systemic corticosteroid.[8,30-34] The main characteristics of these studies are summarized in Table 2. The studies originated in a wide variety of countries, as follows: 4 were from Canada,[21,27,28,32] 1 from the United States of America,[8] 1 from Mexico,[25] 1 from Brazil,[33] 3 from Uruguay,[20,24,34] 1 from South Africa,[7] 1 from Israel,[30] 2 from India,[22,31] 2 from Turkey,[26,29] and 1 from Taiwan.[23] Children and adolescents were the subjects in

11 studies[8,22,23,25-27,29-33] and in 6 studies involved adults.[7,20,21,24,28,34]

## Inhaled Corticosteroids Compared to Placebo

Of the 8 studies included in this category, 6 involved multiple doses of inhaled corticosteroids.[20-22,24-26] Clinical indices or lung function findings demonstrated rapid (2 hours after protocol commencement) and significant differences in favor of the inhaled corticosteroids in 4 studies.[20,22,24,25] Of note is the fact that the inhaled corticosteroids were administered at short intervals (every 10 to 30 minutes) in these 4 studies, whereas the other 2 studies–for which no significant effects were observed despite multiple doses–had substantially lengthier administration intervals (every 60 minutes).[21,26] One of these 2 studies demonstrated a favorable trend in terms of a reduction in hospitalizations following 6 hours of treatment.[21] A significant reduction in the combined hospitalization rates 3 and 4 hours after commencement of the protocols was demonstrated (relative risk, 0.32; 95% confidence interval [CI], 0.17-0.60).[20,22,24] Finally, a single dose of inhaled corticosteroids was administered in 2 studies; an early effect on lung function–at 60 minutes–was observed in 1 of the studies,[7] whereas no difference between groups was observed in the other.[23]

## Inhaled Corticosteroids Plus Systemic Corticosteroids Compared to Systemic Corticosteroids

Of the 3 studies applying this protocol, 2 were based on a single dose of inhaled corticosteroide[27,29] and

1 was based on multiple doses.[28] Curiously, only 1 of the single-dose studies demonstrated an early effect (at 60 minutes) on peak expiratory flow that was favorable to the use of inhaled corticosteroids,[29] although in statistical terms the clinical indices revealed no differences between groups. In both single-dose studies, nonetheless, a favorable trend was evident.[27,29] A trend towards a lower hospitalization rate (after 3 hours of treatment) for patients treated with inhaled corticosteroids was observed in 1 of these studies[27] (7% compared to 20%; $P$=.2). Finally, for the only study in which multiple doses of inhaled corticosteroids were administered, the lack of a significant effect may well have been associated with the application of lengthy administration intervals (60 minutes).[28]

### Inhaled Corticosteroids Compared to Systemic Corticosteroids

Inhaled and systemic corticosteroids used to treat severe asthma were compared in a total of 6 clinical trials–5 involving children and adolescents[8,30-33] and 1 involving adults.[34] Analysis of the 3 studies in which multiple doses of inhaled corticosteroids were administered[8,33,34] revealed a significant level of early effects (2 hours after protocol commencement) in the variables studied (lung function, symptoms and signs, discharges, and admissions). A combined analysis of the same 3 studies in relation to discharge rates 2 hours after protocol commencement revealed that the subjects who had received inhaled corticosteroids were 2.5 times more likely to improve than those who had received systemic corticosteroids (relative risk, 2.56; 95% CI, 1.85-3.53). Since 1 in 6 treated subjects in these studies was discharged, the benefits were clearly substantial (95% CI, 4-10). Of note is the fact that the administration intervals were 10 to 30 minutes. Of the 3 studies based on inhaled corticosteroid single-dose protocols,[30,32,33] no significant differences were observed between groups in 2 of the studies. The third study, however, merits special attention.[32] This well-designed study–of children and adolescents with moderate to severe acute asthma–compared the administration of a single dose of inhaled fluticasone (2 mg) with a standard dose of oral prednisone (2 mg/kg), each administered at the commencement of the protocol. The patients treated with prednisone experienced significantly greater increases in spirometric values and their hospitalization rates were significantly lower. As the only study of those analyzed that demonstrated systemic corticosteroids to be superior to inhaled corticosteroids, it is noteworthy that: *a)* the protocol was based on a single dose of inhaled corticosteroids and *b)* the earliest measurement of the variables was 4 hours after protocol commencement. Prednisone superiority, therefore, may possibly be explained by the fact that the genomic or anti-inflammatory effects of the drug may have already been triggered by the time the variables were measured.

### Conclusions

The aim of this review was to analyze the grounds for the administration of inhaled corticosteroids to patients with asthma exacerbations. According to recent studies on the topical nongenomic effects of inhaled corticosteroids on the increased mucosal blood flow experienced by asthma patients, corticosteroids cause vasoconstriction by enhancing norepinephrine action during synapsis between sympathetic endings and smooth muscle cells in the mucosal vasculature. This has the effect of reducing blood flow and airway obstruction, and the result is a rapid increase in spirometric values and improvement in clinical variables. Nonetheless, it must be remembered that even though the effect is rapid, it is also transient, depends on the dose administered, and increases in direct proportion to blood flow. Furthermore, although the vasoconstrictive effect is not specific, it is more potent with budesonide and fluticasone than with beclomethasone. These factors should be taken into consideration in regard to rational use of inhaled corticosteroids to treat asthma exacerbations. Inhaled corticosteroids should be used concurrently with bronchodilators and should be administered frequently, at short intervals and at high doses in order to maintain the effect over time; fluticasone and budesonide, moreover, are preferable to other inhaled corticosteroids. The evidence from the clinical trials described in this review clearly demonstrates that multiple doses of inhaled corticosteroids administered at short intervals (10 to 30 minutes) result in early benefits (12 hours) in spirometric and clinical variables, irrespective of the initial severity of the asthma. An interesting aspect of many of these studies is the fact that patients who received corticosteroids in suitable doses and at suitable intervals improved more rapidly. This benefit was confirmed in the studies that demonstrated a significant probability of early discharge for subjects administered inhaled corticosteroids as opposed to systemic corticosteroids or placebo. In the studies that involved either administration of a single dose of inhaled corticosteroids, or multiple doses at lengthy intervals, on the other hand, effects were invariably negligible or absent. What would seem to be significant, therefore, is dose distribution over time rather than total dose.

The few studies that included an analysis of subgroups confirmed the relationship between therapeutic response and airway obstruction severity: this would indicate that a better response to inhaled corticosteroids is achieved in patients in whom blood flow is more abundant, airway obstruction is greater, and asthma is more severe.[24,34]

### Strengths and Limitations of the Review

Although this review has endeavored to apply widely accepted methodological criteria, its conclusions are clearly affected by the quality and quantity of the evidence. The literature search was systematic so as to

avoid search bias (i.e., the exclusion of relevant studies). The methodology applied in all the clinical trials included was entirely satisfactory; e.g., they were all randomized, double-blind, and placebo-controlled studies. To minimize possible confusion between genomic and nongenomic effects, the review only included studies in which variables were measured within the first 4 hours of the protocol. Since one of the most important criteria for defining a nongenomic effect is rapidity of onset,[13] our conclusions are based exclusively on early responses. Finally, the selected studies were quite similar in terms of the severity of the asthma of the patients, most of whom had moderate to serious exacerbations.

## Repercussions for Clinical Practice and Research

As mentioned, the treatment of asthma exacerbations requires the correction of hypoxemia using oxygen therapy, alleviation of airway obstruction through repeated bronchodilator administration, and finally, control of airway inflammation–most particularly in patients that respond poorly to the initial treatment–using systemic corticosteroids.[1,3] The evidence thrown up by this review clearly endorses the use of inhaled corticosteroids for the initial treatment of patients–whether children or adults–with asthma exacerbations. Inhaled corticosteroids should not, however, be viewed as replacing systemic corticosteroids, which are considered to be a first-line treatment for asthma.[35] The goal, rather, should be to use inhaled corticosteroids to achieve an additional and early nongenomic effect, which may be particularly beneficial to patients with severe asthma or showing a poor initial response.

The evidence provided in this review would indicate fluticasone or budesonide administration by the inhaled route (either nebulized or using a metered-dose inhaler/spacer), at intervals of a minimum of 10 minutes and a maximum of 30 minutes. Even though there were wide variations in the doses used in the studies described above, the evidence would point to minimum effective doses of either 500 µg of nebulized fluticasone administered every 15 minutes or 800 µg of nebulized budesonide administered every 30 minutes. Doses of 400 µg of budesonide using a metered-dose inhaler/spacer at 30-minute intervals also proved effective, as did large doses administered more frequently: e.g., 500 µg of fluticasone administered at 10-minute intervals via a metered-dose inhaler/spacer. Doses should be administered for at least 90 minutes, although administration for longer periods may lead to greater benefits. Further studies are required, however, to clarify the relationship between administered dose and patient response, as also between dose and the initial severity of the patient's asthma. Finally, although the results in relation to certain of the variables evaluated in this review may incline us to think in terms of significant effects in both the clinical and the statistical sense, further studies with suitable protocols are required, as are quantitative meta-analyses of all currently available evidence.[36]

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