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REVIEW ARTICLE

Inhaled corticosteroids in the treatment of respiratory allergy: safety vs. efficacy

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Abstract

Objective: Review the molecular mechanisms of action, efficacy, and potential side effects associated with inhaled corticosteroids (ICS) in children with persistent asthma.

Sources: Articles in English from MEDLINE. The following terms were used: corticosteroids, inhaled corticosteroids, asthma, children, beclomethasone, fluticasone, budesonide, ciclesonide, growth, adrenal insufficiency, bone mineral density, and oral candidiasis. Treatment guidelines, review articles, controlled trials, meta-analyses, and systematic reviews evaluating the efficacy and the adverse events of treatment with ICS were selected.

Summary of the findings: *In vivo* and *in vitro* studies show that the available ICS have different pharmacokinetic and pharmacodynamic properties that result in different action potentials. ICS also differ as to the systemic and local side effects. The bioavailability of these products is essential in order to determine the incidence of side effects. In general, ICS are capable of controlling asthma, reducing the number of exacerbations, medical consultations, hospitalizations, and the need of oral corticosteroid (applications) bursts. Improvement can also be seen in pulmonary function, especially in patients with recent onset asthma. The most documented adverse effect is transitory decrease of growth rate.

Conclusions: ICS are the main anti-inflammatory agent used to treat persistent asthma. When administered in low doses, they seem to be safe and effective. Patient monitoring allows for early detection of possible side effects associated with ICS.

J Pediatr (Rio J). 2006;82(5 Suppl):S198-205: Children, asthma, inhaled corticosteroids, budesonide, beclomethasone, fluticasone, ciclesonide.

Introduction

Corticosteroids (CS) are used as anti-inflammatory therapy in many diseases, including asthma. Chronic inflammation is associated with increased expression of multiple inflammatory genes, which are regulated by pro-inflammatory transcription factors such as nuclear factor-kappa beta (NF-κβ) and protein activator-1 (AP-1), which bind and activate coactivator molecules (CBP, SRC-1, TIF-2, p300/CBP). Transcription factors are activated in all inflammatory diseases. Coactivators acetylate histones (protein components of chromatin), inducing gene transcription.

Molecular mechanisms of CS action

The anti-inflammatory action of CS is measured by their binding to glucocorticoid receptors (GR) in the cytoplasm. Cytoplasmic GRs generally bind to carrier proteins such as the heat shock 90-kDa proteins (hsp90) and the FK-binding protein that protects the receptor and prevents it from being confined in the nucleus.[1]

Once bound to the GR, CS undergo structural changes that lead to the dissociation of the carrier proteins, exposing nuclear localization signals to the GR. This results in the quick transport of the CS/GR complex into the nucleus, where the complex binds to specific DNA sequences in the gene promoter region (GRE). After binding to receptors in the DNA, CS can promote or inhibit gene expression through processes called transactivation and transrepression, respectively. For example, CS transactivate the beta-2 adrenergic receptor gene, the lipocortine-1 gene, the interleucine (IL)-10 gene, and the NF-κβ (Iκβ–α) inhibitor gene with anti-inflammatory actions. CS also promote the synthesis of two proteins that affect the inflammatory signal transduction pathway: the

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glucocorticoid-induced leucine-zipper protein (GILZ), which inhibits NF-κβ and AP-1[2], and MAP kinase phosphatase-1 (MKP-1), which inhibits p38 MAP kinase. Meanwhile, most of the genes that are transactivated by CS are likely to be involved in side effects, including hypertension, edema, hypocalemia, glaucoma, and diabetes.[3]

Through the mechanism of transrepression, the CS "inhibit" the action of transcription factors AP-1 and NF-κβ, decreasing the production of inflammatory mediators, possibly by inhibiting histone acetylation (HAT). With asthma, there is an increase in HAT activity and some decrease in histone deacetylation (HDAC) activity, which is restored by the treatment with CS. It is accepted that this is the most important mechanism of action of CS on inflammatory diseases.[1,4]

CS inhibit the transcription of various cytokines and chemokines that are relevant to inflammatory lung diseases, including IL-1ß, TNF-α, GM-CSF, IL-4, IL-5, IL-8, and eotaxine.[5] Not only do CS block the synthesis of cytokines, they also block cytokine effect by inhibiting the synthesis of cytokine receptors such as the IL-2 receptor. CS reduce the life span of eosynophyls and of lymphocytes.[5]

Treatment with CS is immunosuppressant and anti-inflammatory, and it also promotes the differentiation of regulatory T cells (CD25+CD4+) through a FOXP3-dependent mechanism. The regulatory CD25+CD4+ T cells represent a population of lymphocytes capable of suppressing the immunological response. The FOXP3 marker is correlated with the expression of the anti-inflammatory cytokine IL-10, and is a marker of the activation of regulatory T cells.[6]

Dose vs. safety

All inhaled CS are absorbed systemically and have dose-related adverse systemic effects. Systemic absorption can occur directly through the lung surface or by swallowing the drug.

Immediately after inhaling the CS with the aerosol doser (pMDI), approximately 10 to 20% of the nominal dose delivered is deposited on the lungs, while most of it lodges on the oropharynx and is swallowed. After absorption in the gastrointestinal tract, the drug passes through the liver before entering the systemic circulation. Some CS, especially budesonide (BUD) and fluticasone (FP), are metabolized (89% and 99%, respectively) the first time they pass through the liver. Therefore, after oral absorption, they enter the systemic circulation as inactive metabolites.[7,8] Most drugs, however, are not efficiently inactivated during first-pass metabolism, and enter the systemic circulation without modifications, resulting in extra-pulmonary side effects.

Deposition on the oropharynx and its undesirable local and systemic effects are significantly reduced if the CS is administered with large volume spacers. Washing the mouth after using the metered dose or dry powder inhalers is also recommended in order to reduce systemic bioavailability (swallowed portion).[9] It is important to not that different CS are metabolized differently. Beclomethasone dipropionate (BDP) is metabolized in the form of beclomethasone monopropionate in many tissues, including the lungs, but there is little information about the formation and absorption of this metabolite in humans.

The dose of CS delivered to the lungs will also be absorbed by the systemic circulation. Absorption through the lung surface is quick, and if the drug is not locally metabolized there could be extra-pulmonary effects, especially with very high doses. Currently there are four CS available for asthma treatment: BDP, BUD, FP, and more recently ciclesonide (CIC). These inhaled CS differ not only in terms of pharmacokinetic and pharmacodynamic properties, but also in terms of potency.

CIC, considered to be a soft steroid, is activated only in the lungs after being inhaled, which ensures fewer adverse effects. CIC in itself is inactive, and needs to be cleaved by specific pulmonary esterases to bind to the GR.[10] This CS has strong anti-inflammatory properties and is practically biounavailable. It is a pro-drug without direct activity and low affinity for GRs. Activated CIC is quickly metabolized and transformed in inactive products.[11]

Inhalation devices

The efficacy of CS depends on the topical activity of the drug that reaches the lungs, while the adverse effects depend on oral deposition and on systemic activity. The drug's systemic activity depends on the amount absorbed by both the gastrointestinal tract and the lungs. The amount of drug delivered to the lungs depends on inhalation technique,[12] on the type of inhaler used, with delivery of different size particles,[13] and on whether or not spacers are used.

Each inhalation device, whether pMDI or dry powder inhaler (DPI), requires specific techniques for suitable intrapulmonary delivery.[14] Inhalation devices are so different from one another that the delivery characteristics of one cannot be extrapolated to the others.[14] The use of spacers can alter the amount of breathable particles (between 1 and 4 µm) that reach the lungs and decrease oropharynx deposition, altering both the therapeutic efficacy and the potential for systemic effects.[15]

In pMDI there is a current trend to replace chlorofluorocarbon propellants with hydrofluoroalkane due to their greater pulmonary deposition, greater efficacy[16] and absence of impact on the ozone layer. Other factors that influence the use of pMDI include the patient's ability to coordinate the delivery of the drug

and its inhalation. The use of valve spacers, however, makes it possible for pMDI to be used even by children younger than 2 years of age.

The dry powder inhaled devices (DPIs = diskhaler, diskus, rotahaler, and turbuhaler) require deep inhalation with an inhalation flow > 60 L/min[14], which is only possible for children older than 6 years of age.

Potency of the inhaled corticosteroids

It is difficult to compare the absolute potency levels of the various inhaled CS considering that the available CS have not been compared in a single study. The potency of a CS or its capacity to produce a pharmacologic response is based on its relative potency determined by various measures such as cutaneous vasoconstriction assays (human skin blanching), receptor binding affinity, lipophilicity, and inhibition of inflammatory cells, mediators, and cytokines. Available *in vivo* and *in vitro* measurements of CS functional activity suggest the following relative potencies: FP > BUD = BDP > triamcinolone acetonide (TAA) = flunisolide (FLU).[17] From a pharmacological point of view, the differences in potency are relatively insignificant unless they translate into clinical efficacy.

The activity of a drug depends on its pharmacokinetic and pharmacodynamic properties. Pharmacokinetics determines the concentration-time ratio at the application site. Pharmacodynamics determines the relationship between the concentration of the drug and its clinical effects. A combination of these two parameters is needed in order to determine the global effect of the drug over time.[18]

The therapeutic index, or clinical efficacy, is the only measurable parameter for comparing new inhaled CS or the new CS/inhaler combination with the existing ones. For that, it is necessary to consider the drug's pharmacokinetics (e.g. affinity with receptor, plasma half-life, distribution volume, plasma clearance, and first-pass liver metabolism rate), pharmacodynamics (e.g. properties of dose-response and duration of action), and the characteristics of each inhalation device (e.g. distribution of particle size, efficacy of pulmonary delivery, and usability) (Table 1). The ideal CS should not only be effective, but also safe, that is, it should have a high therapeutic index.

Since the same receptor mediates the effects of all inhaled CS, the qualitative response resulting from the occupation of GR is similar for all. Therefore, the pharmacodynamics of inhaled CS depends exclusively on receptor affinity. In order to ensure equivalent effects, the differences in affinity can be compensated by controlling the dose, that is, the concentration of the drug at the GR binding site. Since the pharmacodynamics of each inhaled CS depends only on the drug's relative GR binding affinity, and because this difference in affinity can be controlled by dose adjustments, the greatest difference between different inhaled CS should be due to their pharmacokinetic properties (Table 1). The following aspects related to the pharmacokinetics of inhaled CS are considered to be important: bioavailability, clearance, distribution volume, half-life, time of permanence in the lung tissue, lipid conjugation, protein binding, and nature of the CS under consideration (biologically active drug or pro-drug) (Table 1).

A discussion about the bioavailability of inhaled CS should differentiate two types of bioavailabilities – pulmonary and oral – which together make up the total systemic bioavailability. Beclomethasone monopropionate has the highest oral bioavailability (~25%), while FP and the active product of CIC have insignificant oral bioavailability.

Table 1 - Comparison of pharmacokinetic and pharmacodynamic parameters of inhaled corticosteroids (adapted from Cerasoli[11])

Parameters	BDP/BMP	BUD	FP	CIC/desCIC	MF
Oral bioavailability	< 1% / 26%	11%	< 1%	< 1%/< 1%	< 1%
Pulmonary deposition	51% BDP	28%	16%	52% CIC	14%
Local activation	little	none	none	yes	none
Receptor binding affinity	53/1,345	935	1,800	12 / 1,200	1,235
Esterification	none	yes	none	yes	none
Lipophilicity	mod/high	low	high	v. high/v. high	
Protein binding: free fraction	87%:13%	88%:12%	90%:10%	99%:1%	98%:1%
$t_{1/2}$, h	0.5/2.7	2.8	7.8	0.36/3.4	4.5
Vd, L	20/424	183	318	207/897	
Clearance, L/h	15/120	84	69	152/228	53.5

BDP = beclomethasone dipropionate, BMP = beclmethasone monopropionate, BUD = Budesonide, FP = fluticasone propionate, CIC = Ciclesonide, MF = mometasone furoate, $t_{1/2}$ = half-life, Vd = volume of distribution, Mod/high = moderate to high, V. high = very high.

In order to reduce systemic adverse events, an inhaled CS should be eliminated from the systemic circulation as quickly as possible. All inhaled CS are quickly metabolized by the liver (~90 L/h).[19] The drugs that are primarily present in tissues have low serum concentrations and therefore large distribution volumes, while the drugs that are primarily present in the blood present low distribution volumes. FP and the two active pro-drug metabolites present large distribution volumes, which means good tissue penetration, in this case into lung tissue[19] (Table 1).

Half-life is the time required for the drug concentration to drop by 50%. Drugs with high clearance have short half-lives, and drugs with large distribution volumes have longer half-lives.[19] Another way of measuring how long the CS stays in the lung (pulmonary residence time) is by calculating the percentage of the drug absorbed over time. Consistent with its long half-life, PF is absorbed slowly, with a significant amount remaining in the lungs 4 to 8 hours after inhalation. In contrast, BUD quickly disappears in the lungs (Table 1).

Lipid conjugation is another important parameter to evaluate the pharmacokinetics of ICS. Lipid-conjugated ICS is retained in the lungs and is not absorbed by the systemic circulation. The distinction between lipid conjugation and lipophilicity is important. Drugs with high lipophilicity frequently present a high degree of unspecific binding to lipids and proteins, which results in their widespread distribution in tissues. As a result of the large distribution volume, drugs such as PF, which have high lipophilicity, also have a long half-life (Table 1).

Protein binding is important because only CS-free molecules can interact with GR; protein-bound molecules are inactive. BDP, BUD, and FP have similar percentages of free drug (~10%). The active product of CIC (des-CIC) has a protein-binding level greater than 99%, which results in a very low proportion of free drug in the circulation in comparison to other ICS. As a result of this high protein binding, less than 1% of des-CIC entering the systemic circulation is available for potential adverse systemic effects, in comparison to 10% or more for other inhaled CS. Therefore, CIC produces significantly less suppression than other ICS[20] (Table 1).

Clinical efficacy

Three systematic reviews show that BDP, BUD, and FP promote a significant improvement in pulmonary function evaluated based on forced expiratory volume in the first second (FEV_1) and peak expiratory flow (PEF), lower frequency of asthma exacerbations, improvement in the symptoms, and less need of beta-2 agonists in any daily dose, versus placebo[21-23].

The determination of clinical efficacy is dependent on the treatment time stipulated. The symptoms of asthma can show a clear response after a few days, whereas maximum improvement of pulmonary function may require weeks. Furthermore, maximum improvement of bronchial hyper-reactivity may take months after the treatment with CS is begun. The results can also vary depending on the CS dose, the severity of asthma at the start of therapy, and on the exposures to allergens and infectious agents during the study.

The standard doses of inhaled CS for adults and children are listed in Table 2.

Some practical points could be indicated for ICS management[24]:

- In cases of mild/moderate asthma, the dose-response profile is not clear, and in general, the highest benefit is obtained with low/moderate doses.
- With mild/moderate asthma, high doses of PF are followed by a marked increase of side effects in the oral cavity, with little improvement in terms of disease control.
- For patients requiring ICS, a moderate initial dose is just as effective as a high initial dose that is gradually reduced along with clinical stabilization.
- Patients with chronic asthma, especially those that frequently use CS either orally or systemically, benefit from elevated doses of inhaled CS.

Table 2 - Doses (µg/day) of inhaled corticosteroids

Dose	Beclo/Budesonide		Fluticasone		Ciclesonide	
	Children	Adults	Children	Adults	Children	Adults
Low	< 200	< 400	< 100	< 200	80	< 160
Moderate	200 to 400	400 to 800	100 to 200	200 to 400	160	320
High	> 400	> 800	> 200	> 400		> 320

A meta-analysis of 14 comparative clinical trials demonstrated that half dose of FP (as compared to BUD and BDP) was numerically superior in all the trials and statistically superior in four of them when compared with BUD and BDP. Therefore, despite the difficulties with standardization, the trials suggest that when using pMDI, FP is more effective than BDP, TAA, and BUD; however, the efficacy of BUD with turbuhaler is similar to that of FP delivered by pMDI or by diskhaler, and better than that of BDP.[25]

Patients with moderate asthma reach similar levels of asthma control with moderate or high doses of FP. High doses of FP (more than 500 µg/day) are beneficial for chronic patients. On CS-dependent asthmatics, significant reductions can be obtained in the oral CS doses with 2,000 µg FP/day, which translates into an advantage in terms of side effects[26].

Corticosteroids and quality of life

CS improve performance at school and at work, and reduce sleep disturbances associated with breathing symptoms. They are more effective when begun days before the exposure to allergens or irritants and should be used regularly, for periods of time sufficient to keep the patient clinically stable. The advantage of topical applications is the lower occurrence of adverse systemic effects. Nevertheless, all topical CS are systemically absorbed and have a class effect of dose-dependent adverse effects. Treatment should be adjusted so that the minimum dose capable of promoting clinical stability is used.

Adverse effects

The bioavailability of the new ICS is low and most of them are dependent on the inhaled fraction that reaches the systemic circulation after absorption through the lungs. However, various factors are important to determine the clinical and systemic effects and the therapeutic index of the ICS: dose delivered, potency, deposition, receptor affinity and local retention, distribution, clearance, and the individual differences in the response to the GC. The main adverse systemic effects of the ICS are as follows: hypothalamic-pituitary-adrenal axis suppression, bone mineral density, vertical growth, and ocular toxicity (including subcapsular cataract and glaucoma).[11,27]

Hypothalamic-pituitary-adrenal axis suppression

The frequency of secondary adrenal insufficiency due to the suppression of the hypothalamic-pituitary-adrenal (HPA) axis resulting from ICS treatment is very low. A few cases in children have been associated with long-term treatment with PF.[28] There is no consensus regarding the suppressing action of ICS on the HPA axis, and the method used to evaluate this suppression is one of the factors that can affect the interpretation of results. Suppression can be evaluated by 24-hour serial monitoring of serum cortisol levels, by determination of nocturnal or 24-hour cortisol in the urine, and by the adrenocorticotropic hormone (ACTH) stimulation test . Further confounding factors are the equivalence of the ICS doses used and the devices used.

A meta-analysis of studies carried out with adults and children concluded that PF has significantly greater adrenal suppressing potential when compared to BDP, BUD or TAA.[29]

Patients in treatment with a low to moderate dose of ICS (< 400 µg/day of BDP, BUD or TAA, or < 200 µg PF, or 160 µg of CIC) usually do not present significant changes in 24-hour plasma cortisol levels,[30] in urine cortisol, and in the response to the ACTH stimulation test.[31] However, suppression of the HPA axis has been detected (without any clinical expression) when using powder inhalation devices, which increase the amount of drug that reaches the lung even in these lower doses.[32]

CIC, the most recent of the ICS available for clinical use in children, has demonstrated efficacy in asthma treatment and a better profile of side effects when compared to other CS.[33] Considered a pro-drug, CIC is activated locally in the lung by pulmonary esterase activity, which ensures high local concentration and little gastrointestinal absorption. Because of its high sensitivity to hepatic oxidases, CIC has a very short plasma half-life, which reduces systemic exposure to the active drug to a minimum.[11] This low systemic exposure has been shown in recent studies demonstrating the absence of a relevant clinical effect on the HPA axis even with high doses, such as 320 to 1,280 µg[34].

In conclusion, treatment with low or moderate doses (< 400 µg/d) of ICS is usually not associated with suppression of the HPA axis in children. Because of this, the routine monitoring of the HPA axis is not necessary, unless there is evidence of growth suppression. On the other hand, children with chronic asthma who receive high doses of ICS or who have been receiving GC through other routes (topical, intranasal) should have their morning levels of plasma cortisol monitored periodically, even in the absence of increased risk of HPA axis suppression. In the presence of low levels, they should be submitted to the ACTH stimulation test.[19]

Bone metabolism

Because CS increase reabsorption and decrease bone formation, they can cause dose- and age-dependent osteoporosis. Bone turnover is greater in children than in adults. Bone mass/density acquisition begins in childhood

and peaks in young adults. Many factors are identified as capable of interfering with the content of bone mass: sex, nutrition, hereditariness, endocrine factors, and physical activity.

The effects of exogenous CS on bone can be evaluated by biochemical markers of bone metabolism, bone mineral density (BMD), or frequency of fractures. A recent review of ICS effects on bone showed no evidence of changes in bone markers or degradation in children treated with ICS in standard doses.[35] Moreover, elevated doses may cause significant changes in the bone turnover rate, but the occurrence of these changes during the treatment, which his usually short-term, deserves further studies.[27]

Asthmatic children treated with BUD (> 800 µg/day) for longer than 18 months,[36] or BUD (500 µg/day) for 4.5 years,[32,37] or BDP (300-800 µg/day) for 2 years[38] do not present reduction of BMD when compared to those treated with placebo or smaller doses of the respective ICS. In wheezing infants, the use of an intermittent treatment model with inhaled BUD (400 µg/day) did not determine significant changes in BMD.[39] In a recent review of the use of ICS in children with asthma, none of the four trials evaluating BMD presented a significant alteration.[40]

In light of the current studies, there is no evidence that the long-term treatment of children with ICS in low doses is associated with the reduction of BMD or with increased risk of osteoporosis or fracture.[41] However, changes in the total bone mineral content in children treated with high doses of BDP or BUD or PF have been recently documented during 12 months of treatment.[42,43] An experimental assay has documented the absence of effect on bone metabolism with ciclesonide, even in elevated doses.[20]

Linear growth

Growth is a complex, non-homogenous physiological phenomenon that is influenced by many factors: genetics, nutrition, hormones, and others. CS interfere with collagen turnover and with the levels of somatomedin, the final growth promoter, produced by human growth hormone; therefore, these drugs may be associated with growth deficit in children with asthma and long-term treatment with ICS, especially in high doses.[19] This interference is more evident during fast growth phases (spurts) in preschool years and puberty. Asthma, however, in and of itself, can interfere with the growth rate.

To monitor growth rate, knemometry (measurement of lower leg length) is useful to detect changes occurring over a short period of time and stadiometry is useful to detect changes over medium or long-term periods. However, adult stature is the most adequate parameter.[42] Current evidence shows that treatment with ICS (medium/high doses) can induce delay in the growth rate at the start of treatment with BDP[19,21,44] or BUD.[19,22] However, this interference is transitory, since there are no reports of an influence on the adult stature of these patients.[19] A few patients receiving higher doses of BDP or BUD (> 750 µg/day) during 14 weeks presented growth retardation.[45] According to the United States National Asthma Education and Prevention Program, low or medium doses of ICS have the potential to impact growth rate, but the effects are small, non-progressive, and possibly reversible. Furthermore, the adult height reached by asthmatic children with ICS treatment is not different than that reached by non-asthmatic children.[46]

A meta-analysis of 21 trials including 810 patients has compared the stature reached in relation to the treatment with inhaled or oral CS. There was slight growth impairment in those treated with oral CS.[47] The Childhood Asthma Management Program (CAMP) compared the efficacy and safety of long-term treatment (4 to 6 years) with BUD and nedocromil sodium in children with mild to moderate asthma. Treatment with BUD resulted in improved airway reactivity, better control of asthma, and transitory reduction in growth rate.[48] A similar finding was reported by other investigators.[49]

Treatment with PF was evaluated in children with mild asthma, and no interference was observed.[50] On the other hand, Guilbert et al. evaluated 2 years of treatment with PF (176 µg/day) in children aged 2 to 3 years old. In addition to clinical control during the active treatment period, a reduction in growth rate, with partial recovery during the follow-up period, was also recorded.[51] A recent double-blind, placebo-controlled study with children treated with different doses of inhaled ciclesonide did not document changes in either lower leg growth rate or effects on the HAP axis.[52,53]

Ocular toxicity

The risk of subcapsular and nuclear cataract associated with the use of ICS is not significant in pediatric patients with asthma; however, it may be greater in the elderly. Sufficient information concerning the differences in the risk of cataract associated with the different ICS formulations is not available.[19,35]

Local side effects

Local side effects include coughing during inhalation, dry throat, hoarseness, dysphonia, and oral candidiasis[5.4,55] Oral hygiene after ICS use helps reduce these dose-dependent effects. CIC offers a significantly lower chance of local side effects since it is not activated on the oral mucosa. The use of devices can also promote less oropharyngeal deposition.[54,55]

Conclusion

ICS are still the gold standard in long-term anti-inflammatory treatment of persistent asthma in children. The clinical benefits of these agents by far surpass the side effects in patients treated with a low to moderate dose. However, clinical follow-up is still essential for the early detection of side effects.

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