Systemic Corticosteroids for Autoimmune/ Inflammatory Disorders in Children: Clinical Aspects

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Introduction

Glucocorticoids (GCs) are a class of steroid hormones released from the adrenal cortex, and their plasma concentration is controlled by the hypothalamic–pituitary–adrenal axis. Endogenous GCs affect biological processes including growth, metabolism, development, immune function, and stress response. GCs and the derived drugs (named corticosteroids) are widely used as pharmacological agents for the treatment of inflammatory disease, asthma, and immune/rheumatologic diseases. This chapter describes the mechanisms of action of synthetic GCs, prescription methods in immune/rheumatologic diseases, and the management of side effects.

Mechanisms of Action

"Corticosteroids" (GCs and mineralocorticoids) have anti-inflammatory, immunosuppressive, and cytotoxic properties. The anti-inflammatory activity of GCs is higher than natural hormones for a reduced mineralocorticoid activity. The therapeutic effects result from a genomic mechanism calling action from the GC receptor (increased synthesis of anti-inflammatory proteins, decreased synthesis and decreased half-life of RNA messengers coding for inflammatory proteins) and a nongenomic (quick) mechanism with no interaction with a surface receiver that would affect intracellular signal channels (mitogen-activated protein kinases channels, calcium fluxes). This results in a decreased production of proinflammatory

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R. Cimaz (ed.), *Systemic Corticosteroids for Inflammatory Disorders in Pediatrics*, DOI 10.1007/978-3-319-16056-6_3

Table 1 Main molecules: comparison of corticosteroid activity

DCI	Anti-inflammatory activity	Mineralocorticoid effect	Dose equivalence (mg)	Half-life (h)
Hydrocortisone	1	1	20	8–12
Cortisone	1	0.8	25	8–12
Prednisone	4	0.8	5	12–36
Prednisolone	4	0.8	5	12–36
Methylprednisolone	5	0.5	4	12–36
Betamethasone	25–30	0	0.75	36–54
Triamcinolone	5	0	4	

cytokines and chemotactic factors as well as of intercellular adhesion molecules (ICAM-1), inhibition of the differentiation and function of macrophages, synthesis of the prostaglandins and leukotrienes, and production of free radicals. GCs also have important effects on immune response (antigen presentation, lymphocyte proliferation and differentiation) and on apoptosis.

Pharmacology

The structure of prednisolone, a reference GC, is comparable to that of natural hormone, since only a double bond differentiates them. This double bond causes an increase in anti-inflammatory activity and in plasma half-life and a decrease in the mineralocorticoid effect. Prednisone is quickly absorbed in the jejunum and is then converted into prednisolone, an active metabolite, through hepatic 11β-hydroxylation. The plasma concentration peak is obtained within 1–2 h, slows down after meals, and varies according to the type of GC. Plasma cortisol is strongly bound to cortisol-binding globulin and albumin. The binding kinetics is not linear or dose-related, and the clearance is urinary. Natural GCs follow a circadian rhythm of maximum secretion between 6 and 9 P.M. and a minimum secretion around midnight. Therefore, the administration schedule of GCs has an essential influence over pituitary secretion: A dose administered in the morning has a minimum effect, contrary to a dose taken in the evening (Table 1).

Conditions of Prescription and Main Indications (Table 2)

The prescription of GCs over a long period is an important decision in terms of consequences, considering the risks of a diagnostic error (i.e., prescription in case of infections or neoplasia) and inappropriate or delayed initiation that could impact vital or functional prognosis. The effect is suspensive, which exposes patients to quick relapses when interruptions are attempted. The side effects of GCs represent

Table 2 Main indications of corticotherapy for child inflammatory diseases

Disease type	Etiology	Remarks
Rheumatology, systemic disease	Juvenile idiopathic arthritis (JIA)	*Systemic-onset JIA*, macrophage activation syndrome, *uveitis, polyarticular JIA*
	Acute rheumatic fever	
	Juvenile dermatomyositis	
	Systemic lupus erythematosus	Pulse therapy: cardiac, nephrologic, neurological form
	Scleroderma	
	Sarcoidosis	
	Systemic vasculitis, refractory Kawasaki disease, complications of Henoch–Schönlein purpura	
Autoinflammatory	PFAPA syndrome	Treatment of crisis
Digestive	Inflammatory bowel disease, autoimmune hepatitis	
Hematological	Thrombocytopenic purpura, autoimmune hemolytic anemia	
Nephrologic	Nephrotic syndrome, glomerulonephritis	
Neurological	Systemic sclerosis, inflammatory demyelinating polyradiculoneuropathy	
Ophthalmological	*Uveitis*	

PFAPA periodic fever, aphthous stomatitis, pharyngitis, adenitis

a major worry, which justifies their use only after a definitive diagnosis has been made. According to the indication, prescription can be short or long term, preferably orally administered prednisone or prednisolone and sometimes with intravenous boluses [1]. Short treatments last less than 10 days and typically aim for an anti-inflammatory effect with high doses (2 mg/kg/day). Examples of such treatment are complicated Henoch–Schönlein purpura, Kawasaki syndrome resistant to immunoglobulins, and idiopathic thrombocytopenic purpura. Long-term treatments aim for lower doses (maximum 60–80 mg/day), with a quick taper. The initial dosing, preferably in the morning, is generally maintained 2–4 weeks, and carefully tapered in gradual steps from 1 to 4 weeks, depending on the pathology, the protocol, and the initial response. This decrease will occur faster for dosages higher than 1 mg/kg/day, with the objective of reaching a maintenance dose of 0.5 mg/kg/day and then the minimal effective dose or the discontinuation. Alternate-day dosing as used for nephrotic syndrome may attenuate the effects on growth but in other indications represents a risk of disease flare. GCs should never be interrupted abruptly, since the risk of adrenal insufficiency must be considered when the administered dose is greater than the replacement dose and when treatment exceeds 15 days. High-dosage "pulse" therapy allows one to obtain a quick anti-inflammatory effect, possibly with a corticosteroid-sparing effect. Intravenous boluses are usually

recommended daily over 3 consecutive days, particularly in critical situations regarding vital or functional prognosis (severe organ involvement, hemophagocytosis, resistant Kawasaki disease). Methylprednisolone is given via an intravenous route at a dose of 30 mg/kg (max. 1 g) over a period of at least 4 h and while carefully monitoring vital signs. Intra-articular injections can be part of the therapeutic strategy for juvenile arthritis. Triamcinolone hexacetonide is the most used form because of its long-lasting effect [2].

How to Limit the Main Side Effects of GCs

GCs possess several endocrinological properties, being involved in many physiological and pathological processes; their efficacy in improving inflammatory disorders results from the pleiotropic effects of the GC receptors on multiple signaling pathways. Adverse effects include growth retardation, immunosuppression, hypertension, hyperglycemia, inhibition of wound repair, deleterious effects on bone and cartilage, metabolic disturbances (lipid and protein metabolism, muscle wasting), hydro-electrolytic imbalance, gastritis, premature atherosclerosis, and ocular (glaucoma and cataract) and dermatologic (acne, alopecia, hypertrichosis, stretch marks) complications.

Metabolic Complications

The prevention of metabolic complications (carbohydrate intolerance, hypertriglyceridemia, adiposity, protein hypercatabolism) mainly includes a dietary plan based on a hypocaloric, hyperproteic, low-salt regimen, free from quick-absorption sugars and prepared as menus adapted to the energy requirements and food habits of children.

Osteoporosis

GC-induced osteoporosis (GIO) is the most common form of iatrogenic osteoporosis and one of the most common forms of secondary osteoporosis. Fracture risk increases markedly in the first 3 months after GC initiation and decreases after discontinuation, but the risk does not return to baseline. GCs adversely affect bone strength/quality in a number of ways: They induce an imbalance between bone formation and resorption, with short- (demineralization) and long-term consequences. They inhibit bone formation (by increased apoptosis of osteoblasts and osteocytes, decreased osteoblastogenesis, and disruption of bone remodeling regulation) and they increase bone resorption (by enhanced osteoclast survival and osteoclastogenesis). Moreover, they decrease intestinal calcium absorption and increase urinary calcium excretion. Thus, GCs decrease bone mass (12 % for the first 3 months, then 3 %/year) and

increase the fracture risk mainly of vertebrae [3, 4]. Prevention of osteoporosis consists in controlling the underlying inflammatory disease, sparing corticosteroid dosage, promoting physical activities, and recommending calcium intake in relation to the patient's age. In case of insufficiency, the addition of a calcium supplement at doses between 300 (<5 years) and 500 mg/day (>5 years) is important. Vitamin D supplementation, as a daily (400 UI/day at least) or quarterly (80,000 or 100,000 UI) recommendation, has the objective of obtaining a serum level of 25-OH-D3 between 20 and 40 ng/ml. Beyond 3 months of corticosteroid treatment, it is advisable to perform a reference densitometry (DXA) and monitor the Z score according to its initial value, the status of inflammatory disease, and the dose and duration of GC therapy. An evaluation of bone density and metabolism can be typically proposed in severe cases once to twice a year. The use of bisphosphonate therapy for children is still under discussion. It is recommended only after specialized advice in cases of fractures, bone pain, or quick degradation of bone density.

Growth-Retarding Effects

A growth delay is unavoidable beyond 0.3 mg/kg/day (resistance to growth hormone, decrease of growth hormone and insulin-like growth factor-1, serum levels, action on growth plate). Other factors, for example, inflammatory and nutritional factors, also play a role. In some situations, growth hormone treatment may be discussed [5].

Infections

The risk for community-based and/or opportunistic infections is very high at dosages exceeding 2 mg/kg/day for more than 15 days, or after repeated intravenous boluses. However, other predisposing factors such as the inflammatory disease, malnutrition, hyperglycemia, and concomitant immunosuppressors should be considered. It is advisable to inform patients and their families about the need for an early consultation in case of fever, about environmental risks (e.g., unpasteurized foods, uncooked meats), contact with animals, and travels to endemic areas for unusual pathogens such as histoplasmosis. Observance of the immunization schedule is essential, and flu vaccines and pneumococcal vaccines are especially recommended. Live vaccines are contraindicated while on chronic corticosteroid treatment. Continuous trimethoprim-sulfamethoxazole may be recommended as a prevention of *Pneumocystis jirovecii* infection. Herpes virus infections warrant early treatment with acyclovir. Contact with varicella for a high-risk child requires administration within 4 days of specific anti-VZV immunoglobulins, which is the most commonly recommended approach. If not possible, chemoprophylaxis with acyclovir (80 mg/kg/day, divided into four doses, for 7 days) starting between the seventh and tenth day after the exposure should be proposed.

Psychiatric Disturbances

GCs are mediators of stress response. Steroid receptors are expressed in different areas of the brain and their role is related to the regulation of various neurotransmitters, including serotonin and dopamine. In particular, in the central nervous system, GCs exert their potential effects at the hippocampal level, a structure intimately involved in the limbic system, which provides the processing of emotional information and memory. Behavioral changes and mood disorders (irritability, agitation, anxiety, insomnia, and depression) are frequent and difficult to predict and sometimes to distinguish from symptoms related to the underlying illness [6]. Increased appetite with a resulting increase of body weight is frequent. Psychotic conditions (mania, psychosis, and delirium), nearly always transient, have been described but remain rare. Sleep disorders can be limited by administration of GCs in the morning.

Conclusion

In recent years, patient management for inflammatory diseases has seen considerable improvements due to new and effective therapies. However, GCs still remain the reference treatment for many disorders. The administration of GCs is an important decision, which should be taken within a precise treatment plan and with clear objectives. Parents and families should be informed of this plan and of the possible risks and benefits. We should always aim to find a balance between sufficient anti-inflammatory activity and acceptable undesired effects, which must be monitored and prevented when possible.

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