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CLINICAL PHARMACOLOGY OF GLUCOCORTICOID DRUG USE IN CHILDREN OLDER THAN 2 YEARS

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Abstract. This article presents an in-depth review of the clinical pharmacology of glucocorticoid therapy in pediatric patients older than two years. Glucocorticoids are among the most widely prescribed medications in childhood for their potent anti-inflammatory, antiallergic, and immunosuppressive properties. However, their clinical use requires a delicate balance between therapeutic efficacy and potential adverse effects on growth, metabolism, and endocrine function. This paper examines the pharmacokinetics and pharmacodynamics of glucocorticoids in children, the molecular mechanisms of action, therapeutic indications, dosing considerations, adverse reactions, and strategies for minimizing toxicity. Special emphasis is placed on age-related physiological differences, hypothalamic–pituitary–adrenal (HPA) axis suppression, and the long-term implications of systemic or inhaled glucocorticoid use.
Keywords: glucocorticoids, pediatric pharmacology, corticosteroid therapy, HPA axis suppression, growth retardation.

INTRODUCTION

Glucocorticoids represent one of the most significant pharmacological discoveries of the twentieth century, and their clinical utility remains unparalleled in the management of inflammatory, allergic, autoimmune, and neoplastic disorders. In pediatric medicine, they are indispensable for conditions such as asthma, croup, nephrotic syndrome, juvenile idiopathic arthritis, and acute lymphoblastic leukemia. Yet, their use in children, particularly those older than two years, requires precise clinical judgment and understanding of the unique aspects of pediatric physiology. Children are not “small adults”; they differ markedly in drug absorption, distribution, metabolism, and elimination. These differences profoundly influence the pharmacokinetics of glucocorticoids, as well as their systemic impact on growth and endocrine regulation [1].

The primary challenge in pediatric glucocorticoid pharmacology is to achieve sufficient anti-inflammatory activity while minimizing interference with normal growth, bone metabolism, and immune maturation. Chronic exposure to

glucocorticoids, even at moderate doses, may result in growth suppression, obesity, adrenal insufficiency, and increased susceptibility to infection. Therefore, pediatric clinicians must understand not only the therapeutic potential of these drugs but also their molecular and physiological consequences during early childhood development.

MATERIALS AND METHODS

Glucocorticoids exert their biological effects through complex genomic and non-genomic pathways. After entering the cell, they bind to cytoplasmic glucocorticoid receptors (GRs), forming an activated receptor–ligand complex that translocates to the nucleus and binds specific DNA sequences known as glucocorticoid response elements (GREs). This binding modulates the transcription of numerous target genes: upregulating anti-inflammatory proteins such as lipocortin-1 and inhibiting proinflammatory mediators like cytokines, prostaglandins, and leukotrienes. The non-genomic actions of glucocorticoids, mediated through membrane-associated receptors and secondary messengers, contribute to their rapid anti-inflammatory effects, especially in acute conditions such as asthma exacerbations or allergic reactions [2].

In children, these mechanisms are particularly relevant because their immune system is still developing. Over-suppression of inflammatory responses may lead to impaired immunity or delayed tissue repair. Moreover, glucocorticoids interfere with the hypothalamic–pituitary–adrenal axis by exerting negative feedback at the level of the hypothalamus and pituitary gland, thereby reducing endogenous cortisol production. This suppression can become clinically significant with prolonged or high-dose therapy and may persist for months after drug withdrawal.

RESULTS AND DISCUSSION

The pharmacokinetics of glucocorticoids in children differ significantly from those in adults due to age-related changes in hepatic enzyme activity, plasma protein binding, and renal clearance. After the age of two, hepatic cytochrome P450 enzymes (especially CYP3A4) become more active, resulting in faster metabolism of certain corticosteroids such as prednisolone and dexamethasone. Consequently, children often require proportionally higher doses (on a mg/kg basis) to achieve comparable plasma concentrations and therapeutic effects. However, interindividual variability is considerable, necessitating careful titration [3].

Protein binding is another important determinant of glucocorticoid pharmacokinetics. Cortisol and synthetic glucocorticoids are primarily bound to corticosteroid-binding globulin (CBG) and albumin. In young children, CBG concentrations are slightly lower than in adults, increasing the proportion of free, pharmacologically active drug. Enhanced renal clearance in this age group also contributes to shorter elimination half-

lives. These factors underline the necessity of individualized dosing regimens and monitoring, particularly for long-term therapy.

Glucocorticoids are used in pediatric patients for a broad spectrum of diseases. Systemic administration (oral or intravenous) is essential in severe inflammatory or autoimmune conditions such as nephrotic syndrome, systemic lupus erythematosus, or acute lymphoblastic leukemia. Inhaled glucocorticoids such as budesonide and fluticasone are the cornerstone of long-term asthma control, while topical preparations (hydrocortisone, betamethasone) are widely used in dermatologic disorders. Intranasal formulations treat allergic rhinitis, and intra-articular injections may be employed in juvenile arthritis.

The route of administration significantly influences both efficacy and safety. Inhaled and topical routes minimize systemic exposure and reduce the risk of HPA axis suppression, yet chronic or high-dose use can still result in systemic absorption. Oral and intravenous routes, though potent, carry greater risks for adverse metabolic and endocrine effects and must be accompanied by gradual tapering schedules to prevent adrenal insufficiency.

The adverse effects of glucocorticoid therapy in children are dose-dependent and related to both the duration and potency of exposure. The most concerning long-term complication is growth suppression, resulting from inhibition of growth hormone secretion, decreased osteoblast activity, and suppression of insulin-like growth factor-1 (IGF-1) production. Skeletal demineralization and osteopenia are also common due to decreased calcium absorption and increased bone resorption [4].

Metabolic disturbances include central obesity, glucose intolerance, and dyslipidemia, collectively known as “Cushingoid features.” Immunosuppression increases the risk of bacterial, viral, and fungal infections. Behavioral and neuropsychiatric changes—such as mood swings, irritability, or even psychosis—have been reported in susceptible children. Prolonged use may lead to HPA axis suppression, causing adrenal atrophy and an impaired stress response, which can be life-threatening during illness or surgery if not properly managed. For this reason, withdrawal from long-term glucocorticoid therapy must be gradual, allowing endogenous cortisol production to recover.

The guiding principle in pediatric glucocorticoid therapy is the “lowest effective dose for the shortest possible duration.” Alternate-day dosing can reduce HPA axis suppression, particularly in chronic inflammatory diseases. When long-term therapy is unavoidable, clinicians often opt for intermediate-acting agents like prednisolone, which more closely mimic physiological cortisol rhythms. The use of inhaled corticosteroids with high first-pass hepatic metabolism (such as fluticasone) reduces

systemic exposure and side effects. Additionally, nutritional support with adequate calcium, vitamin D, and protein intake helps mitigate the risk of bone loss. Regular growth monitoring, blood pressure measurement, and assessment of infection risk are mandatory for children receiving long-term treatment [5].

Recent pharmacological research has aimed to separate the beneficial anti-inflammatory effects of glucocorticoids from their metabolic side effects. The development of selective glucocorticoid receptor agonists (SEGRAs) seeks to maintain transrepression (anti-inflammatory gene suppression) while minimizing transactivation (metabolic gene stimulation). Furthermore, nanotechnology-based drug delivery systems, such as liposomal formulations, promise to target inflamed tissues more selectively, reducing systemic exposure. These innovations, coupled with pharmacogenetic insights into CYP3A4 polymorphisms and glucocorticoid receptor variants, hold the potential to personalize therapy and minimize toxicity in pediatric populations.

CONCLUSION

The clinical pharmacology of glucocorticoids in children older than two years reflects a constant interplay between therapeutic benefit and physiological vulnerability. While these agents remain essential in managing many pediatric diseases, their power demands meticulous control. Every decision to initiate, maintain, or taper therapy must consider not only the immediate inflammatory response but also the long-term impact on growth, metabolism, and neuroendocrine function.

Children’s heightened metabolic rate, faster hepatic clearance, and developing endocrine system make them particularly sensitive to both the therapeutic and adverse actions of glucocorticoids. Awareness of these differences, coupled with careful dosing and monitoring, allows clinicians to harness the full potential of glucocorticoid therapy without compromising safety. The emergence of selective receptor modulators and targeted delivery technologies promises to refine the balance between efficacy and toxicity further.

Ultimately, glucocorticoid therapy in pediatric patients is a paradigm of individualized medicine — a practice that demands not only pharmacological expertise but also empathy and vigilance. The clinician must remain aware that each milligram of a corticosteroid can profoundly shape a child’s growth trajectory and physiological development. Therefore, the art of pediatric pharmacology lies not in prescribing more, but in prescribing wisely — achieving control of disease while preserving the child’s future health and potential.

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