Strategies for Minimizing Corticosteroid Toxicity: A Review

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ABSTRACT

Glucocorticoids (GCs) are used commonly for the treatment of various pediatric inflammatory and autoimmune diseases. Although potent and generally effective, they are not without risks for producing serious adverse effects, especially when used in high doses for prolonged periods of time. For proper use of systemic glucocorticoids, a basic knowledge of the pharmacology, clinical usage guidelines, and adverse reactions of these agents is imperative. This review article emphasis on the commonly observed side-effects encountered with GC use in children and their underlying basic pathophysiological mechanisms. The appropriate anticipation of these side-effects with timely implementation of the suggested evidence-based guidelines has the potential significantly to prevent, minimize and treat common and disabling complications of glucocorticoid therapy. [Indian J Pediatr 2008; 75 (10) : 1067-1073] E-mail : surjitsinghpgi@rediffmail.com

Key words : Glucocorticoid; Toxicity

Glucocorticoids are important regulators of diverse physiological systems and are often used in the treatment of a wide variety of pediatric inflammatory, autoimmune, and neoplastic diseases. Hench, in 1949, was the first to report on the beneficial effects of adrenocorticotropic hormone and cortisol in patients with rheumatoid arthritis. It is estimated that as many as 10% of children may require some form of glucocorticoid at some point of their childhood. Although the indications for glucocorticoids in these various conditions are clear, the treating physician must be aware of the potential side effects. Recent advances in development of glucocorticoid or glucocorticoid receptor ligands have improved therapeutic effect/adverse reaction ratio.

For proper use of systemic glucocorticoids, a basic knowledge of the pharmacology, clinical usage guidelines, and adverse reactions of these agents is imperative. The major purpose of this review is to provide a practical approach to increasing efficacy and minimizing side effects of glucocorticoid therapy.

Pathophysiology of glucocorticoid mediated side effects

The underlying molecular mechanisms for glucocorticoid mediated side effects are complex and only partly understood. Recent data suggest that certain side effects are predominantly mediated via transactivation (e.g., diabetes, glaucoma), whereas others are predominantly mediated via transrepression (e.g., suppression of the hypothalamic-pituitary-adrenal axis). For conditions like osteoporosis the underlying mechanisms are more complex.¹

Selection of an appropriate glucocorticoid

The drug duration/dosage should take into account the risk/benefit ratio. The adverse effects depend on these parameters as well as on idiosyncratic factors. As a rule of thumb, it can be stated that duration of steroid therapy is of greater importance than the dose administered. Side-effects are usually more severe after systemic than topical application. Commonly encountered side effects are enumerated in table 1.

General principles for minimizing glucocorticoid toxicity

a) There should be definite indication to start GC treatment.
b) Use short- and intermediate-acting GCs in preference to longer acting ones.
c) Use minimum necessary dose and duration of treatment.
d) Once-a-day morning administration should be preferred over divided dose therapy.
d) Use targeted therapy like inhaled corticosteroids in asthma.

e) Rinse mouth after use of inhalational steroids.

f) Use steroid sparing agents (immunosuppressants) wherever applicable.

g) During treatment monitor for body weight, height, blood pressure, serum lipids, blood and/or urine glucose and ocular pressure and development of cataract.

h) Careful withdrawl after long term steroid administration.

i) Beware of drug interactions eg reduced levels of GC occurs with concomitant use of Rifampicin.

**Specific therapies to prevent systemic toxicity:**

(a) **Bone**

i) **Pathophysiology:** One organ system that has the potential to be profoundly affected by glucocorticoids is the skeleton and glucocorticoids-induced osteoporosis (GIO) is the most common form of secondary osteoporosis. Glucocorticoid impair the replication, differentiation and function of osteoblasts and induce the apoptosis of mature osteoblasts and osteocytes. These effects lead to a suppression of bone formation, a central feature in the pathogenesis of GIO. Glucocorticoids also favor osteoclastogenesis and as a consequence increase bone resorption (Table 2).

(ii) **Clinical relevance:** Since glucocorticoidss have their strongest effect on cancellous bone, fractures are more common in vertebral bodies and ribs. In our experience, however, rib fractures are rarely encountered in children on long term glucocorticoid therapy. Because demineralization of bone is not detectable on conventional radiographs until at least 30% of the bone mineral density is lost, osteoporosis is best diagnosed by documenting decreased bone mineral density, using a bone densitometer. Despite the fact that glucocorticoids can cause bone loss and fractures, many patients receiving or initiating long-term glucocorticoids therapy are not evaluated for their skeletal health. Furthermore, patients are usually not counseled regarding specific preventive or therapeutic agents when indicated.

(iii) **Strategies to prevent development of glucocorticoid induced osteoporosis (GIO):** A number of approaches for the prevention of GIO have been studied in adults but knowledge about similar interventions in children are still limited. Supplementation with calcium and vitamin D, or an activated form of vitamin D may be offered to all children receiving glucocorticoids since several open studies suggest that some children with rheumatic disease receiving glucocorticoids may also benefit from calcium and vitamin D.

(iv) **Strategies for treatment of established osteoporosis:** Treatment of osteoporosis consists of attempting to decrease the glucocorticoid dose and/or frequency, increasing calcium intake, providing

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<thead>
<tr>
<th>Bone cells</th>
<th>Effects of glucocorticoids</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Osteoblasts</td>
<td>↓ function, ↑ apoptosis, ↓ differentiation</td>
<td>↓ bone formation</td>
</tr>
<tr>
<td>Osteoclasts</td>
<td>↓ genesis, ↓ apoptosis</td>
<td>↓ boneresorption</td>
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