Brief

Corticosteroids

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> Corticosteroids are one of the most important classes of anti-inflammatory and immune modulators in a physician's arsenal to help treat a variety of conditions. They also have significant adverse effects with short- and long-term use and, therefore, need to be prescribed judiciously. This article briefly reviews the uses and adverse effects of corticosteroids.

> Corticosteroids have been used to treat a wide range of diseases, including allergic, dermatologic, gastrointestinal, and hematologic/oncologic disorders; some infectious diseases; organ transplant; renal disease; and respiratory and rheumatologic disorders. In some cases, such as acute asthma exacerbations, a short course of oral corticosteroids is used for 3 to 5 days. In other situations, patients need to take corticosteroids for much longer, sometimes months to years. In general, if someone has been receiving systemic corticosteroids for less than 10 to 14 days, it is deemed safe to vaccinate him or her, including with live viral vaccines, per the *Red Book*. However, it is recommended to try to limit the duration to the shortest time possible and the amount/dose of corticosteroids to the lowest potency to achieve the desired results.

ADVERSE EFFECTS WITH LONG-TERM USE

There are many adverse effects due to long-term use of corticosteroids, defined as continued use of oral or intravenous corticosteroids for more than 14 days. With several important exceptions, most of these effects are reversed or partly reversed with discontinuation of the corticosteroid medication. However, cataract formation, earlier development of atherosclerotic disease, and bone abnormalities (osteoporosis and osteonecrosis) are, in general, unchanged by stopping medication. The adverse effects of long-term corticosteroid use are many and include the aforementioned osteoporosis and cataract formation, in addition to hypothalamic-pituitary-adrenal (HPA) axis suppression, cushingoid appearance with weight gain, diabetes, cardiovascular disorders, elevation of cholesterol level, immunosuppression, behavioral changes (such as aggressive behavior, inattentiveness, mood swings, and sleep disturbances), gastrointestinal problems (gastritis and gastrointestinal bleeding), and skin manifestations (skin thinning, ecchymoses, acne, and striae). Finally, growth suppression is a problem that is unique to the pediatric population.

A variety of studies of children with chronic medical disorders have been published showing that children's final height is less than would have otherwise been expected when taking long-term systemic corticosteroids. One study looked at children with cystic fibrosis who were placed on either every-other-day prednisone treatment versus placebo. The children were followed for many years after stopping treatment, and boys, in particular, were found to be significantly shorter compared with those receiving placebo after 18 years of age.

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A systematic review of studies that looked at adverse effects of long-term use of corticosteroids in children was recently published. The reasons for corticosteroid use varied and included leukemia, respiratory diseases such as asthma and cystic fibrosis, nephrotic syndrome, and Crohn's disease. According to this review, the most common complications seen with oral corticosteroid therapy were weight gain, growth suppression, and features of Cushing syndrome. In addition, when tested, more than half of the children showed HPA axis suppression. Several of these children did not regain appropriate adrenal function for up to 4 to 8 months after withdrawal of corticosteroids. The most common reason for stopping the corticosteroid medication was behavioral changes. In I particular study that looked at long-term use of corticosteroids in children diagnosed as having leukemia, patients who were older (>10 years) and were taking dexamethasone versus prednisone were more likely to be immunosuppressed.

The most serious complication noted in this systematic review was increased susceptibility to infection, which resulted in several deaths. Compared with the incidence of infection reported with short-course oral corticosteroids, the risk of infection was much greater with long-term use of corticosteroids (8.7% versus <1%). The most frequent culprit in deaths due to infection was found to be varicella.

ADVERSE EFFECTS WITH SHORT-TERM USE

Although there are widely known adverse effects to longterm use of corticosteroids, there are adverse effects to short courses of systemic corticosteroids as well. A recent systematic review of adverse effects of short courses of corticosteroids (<14 days) was published. The most serious adverse effect was infection due to immunosuppression, which occurred less than 1% of the time. The most common infection was again due to varicella. The more common adverse effects of short courses of corticosteroids included vomiting, behavior changes, and sleep disturbances, in order of decreasing frequency. Vomiting was associated with larger doses of corticosteroids and was noted, in particular, with use of oral prednisolone. The higher the dose, the more likely the patient would experience vomiting. This was the leading cause of patient nonadherence to corticosteroid treatment. A similar dose effect was seen with behavioral changes (anxiety, hyperactivity, and aggressive behavior), with these changes seen more frequently with higher doses of corticosteroids. In studies that

documented blood pressure and weight, almost one-third of children experienced blood pressure elevation and weight gain, although these adverse effects were noted to be transient and resolved after discontinuation.

ADVERSE EFFECTS OF INHALED CORTICOSTEROIDS

Although inhaled corticosteroids, which are the mainstay of therapy for children with persistent asthma, are believed to have fewer adverse effects than systemic corticosteroids, adverse reactions still occur. Local adverse effects include oral candidiasis, cough, hoarse voice, and dysphonia. All of these are dose related and can be somewhat mitigated by using a spacer with a metered dose inhaler and rinsing the mouth immediately after use.

Systemic adverse effects of inhaled corticosteroids depend on the dose administered, how the medication is delivered (dry powdered inhaler, metered dose inhaler with and without spacer, nebulized medication), and the individual patient's response to corticosteroid therapy. HPA axis suppression has been found in children who are taking high dosages of inhaled corticosteroids as well as long-term use (>6 months' duration). In addition, growth suppression has been noted in children who used inhaled corticosteroids for longer than 12 months. Although some studies seemed to show that children using inhaled corticosteroids for varying periods ultimately obtained their normal adult height, a meta-analysis showed that the initial loss of height during the first year of inhaled corticosteroid use was never recovered. Bone density mineralization and fractures do not seem to be associated with low- to medium-dose inhaled corticosteroids; however, this can be complicated by the fact that children with persistent asthma also receive courses of systemic corticosteroids during acute exacerbations.

RECOMMENDATIONS FOR MONITORING

In general, patients receiving long-term systemic corticosteroids should be monitored at least every 6 months, and children younger than 2 years should be monitored every 3 months. A baseline assessment should include weight, height, blood pressure, complete blood cell count, glucose level, lipid levels, and consideration of a bone density test. In addition, pubertal status and growth should be closely monitored. Currently there are no established guidelines, to our knowledge, regarding when to assess a patient for HPA axis suppression. HPA axis suppression does occur when children have received systemic corticosteroids for more than 2 weeks. In addition, physicians should be aware that children who have received high-dose inhaled corticosteroids (equivalent to >500 μ g/d of fluticasone) can also be at risk for HPA axis suppression if linear growth seems to be affected. Clinicians should use their judgment as to when to perform HPA axis testing. Questions regarding possible symptoms of diabetes should be asked, and patients should be referred for an annual ophthalmologic examination to check for cataracts or glaucoma. Patients and families need to be counseled to seek medical attention for any sign of infection. Stress dosing of corticosteroids needs to be considered to help prevent adrenal crisis. If the child has minor stress, such as a viral infection, low-grade fever, or minor surgery, the dose of corticosteroids should be doubled. For situations considered major stress, such as severe infection or major surgery, the child should be given hydrocortisone intravenously/intramuscularly 100 mg/m² followed by 25 mg/m² every 6 hours, and an endocrinologist should be consulted. The family must be educated about this possibility and should carry documentation of medications taken to prevent any possible oversight because this could lead to adrenal crisis. When the plan is to discontinue corticosteroids, tapering of corticosteroids should be initiated when children have been receiving long-term courses of corticosteroids.

In summary, corticosteroids are an extremely effective class of medications that play a role in the management of many chronic diseases. However, the adverse effects of corticosteroids can be quite serious. Every effort should be made to minimize the duration of treatment and the amount/dosage of corticosteroids needed. Close monitoring of potential adverse effects is imperative. **COMMENT:** This *In Brief* really made me pause and think of all the patients I have cared for who have been prescribed corticosteroids with various doses and durations of treatment. As primary care health providers care for more children with chronic medical conditions, it is critical to know the benefits, adverse effects, and monitoring strategies of patients taking corticosteroids, as the author of this In Brief outlines so well. As with any medication, balancing the lowest-potency dose and shortest duration that still provides the desired medicinal benefits is critical to minimize morbidity. Although corticosteroids are important medications, their potential adverse effects are multiple and may vary by patient. The possible effect on bone health is significant for children in age groups and with chronic medical problems who are already at risk. Also, it is important to remember that corticosteroids have 2 properties: immunosuppression and anti-inflammatory responses that can affect a body's response to infections. Vigilance by parents, patients, and health-care providers for the possible development of infections is essential because the immunosuppression effect can lead to more virulent infections with common viruses, vet the anti-inflammatory properties can lead to a modification of symptoms and subsequent delay in diagnosis of these infections. The primary care provider has a critical role in both judicious prescribing and partnering with subspecialists to ensure that their shared patients with chronic medical problems are being monitored for adverse effects while also ensuring the shortest duration of exposure to corticosteroids as warranted by their symptoms and disease.

> - Janet R. Serwint, MD Associate Editor, *In Brief*

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