

Monitoring Adverse Reactions to Steroid Therapy in Children

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Patients on corticosteroid therapy, specially for a long period are likely to develop many adverse effects related to the therapy. A physician should be conversant with these to ensure early detection, management and prevention, where possible. Thus, all patients on a long-term corticosteroid therapy should have a baseline and 3 monthly assessments for weight, height, blood pressure and other clinical features of Cushing's syndrome. A 2 hours postprandial blood sugar and serum electrolyte estimation should also be included. Ophthalmic evaluation for glaucoma and cataract should be carried out at 6 monthly intervals and densitometry annually for early detection of osteopenia. In addition, a high index of suspicion should be maintained for timely detection of infections, avascular bone necrosis, myopathy and pseudotumor cerebri.

Key words: *Adverse effects, Cortico-steroids*

Corticosteroids (CS) are amongst the most commonly employed drugs in clinical practice. They are used for substitution therapy in adrenal insufficiency, or for suppression of adrenal androgen secretion in diseases characterized by androgen hypersecretion like congenital adrenal hyperplasia.

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In addition, they are also used in gastrointestinal, respiratory, neurological, autoimmune, collagen, renal, ophthalmic, hematological and neoplastic diseases to achieve pharmacological effects not necessarily related to their normal physiological role. The agents used include naturally occurring glucocorticoids cortisone and cortisol (hydrocortisone), and their synthetic derivatives.

The goal of CS therapy is to obtain maximum clinical benefit with a minimum of adverse effects. While cortisone and hydrocortisone have significant mineralo-corticoid activity, most potent synthetic CS like dexamethasone and methyl prednisolone are virtually devoid of mineralocorticoid activity (except fluodrocortisone, which is primarily used as mineralocorticoid). Prednisone and prednisolone fall somewhere in between and have some mineralocorticoid activity. Thus, systemic side effects of CS are primarily those related to glucocorticoid excess, or to suppression of hypothalamo-pituitary-adrenal (HPA) axis function.

Important adverse reactions that may occur during CS therapy in children are listed in *Table 1*. A brief description including their incidence, early recognition and management follows:

Endocrine/Metabolic Effects

Cushing's Syndrome

Exogenous steroid administration is the commonest cause of Cushing's syndrome. Its development depends upon the dose, route of administration and duration of therapy. With high dose steroid therapy, signs and symptoms may be observed within a month(2). On the

TABLE I—*Important Adverse Effects of Corticosteroids*(1)

1. Endocrine/metabolic,
(a) Iatrogenic Cushing's syndrome
(b) Hyperglycemia
(c) Suppression of hypothalamo-pituitary-adrenal axis
(d) Growth retardation
2. Cardio vascular
(a) Hypertension
3. Gastrointestinal
(a) Gastric ulcers
(b) Gastric hemorrhage
(c) Pancreatitis
4. Ophthalmic
(a) Sub-capsular cataract
(b) Glaucoma
(c) Others
5. Musculo-skeletal
(a) Osteoporosis
(b) Avascular necrosis
(c) Myopathy
6. Immune function
(a) Susceptibility to infection
7. Neuropsychiatric
(a) Alteration in mood or personality
(b) Psychosis
(c) Pseudotumor cerebri

other hand, this complication may also supervene with long-term use of even small amount of steroids. Iatrogenic Cushing's syndrome differs from the idiopathic form in a few important aspects (*Table II*). Since it is associated with other major complications like fluid and water retention, poor wound healing and osteopenia, patients on chronic treatment should adhere to a potassium rich diet with caloric restriction, high protein and low sodium. Younger children (<2 yrs) should be monitored every 3 months, and others every 6

months by measurement of weight, length/height, blood pressure, 2 hours post-prandial blood glucose and serum electrolytes(3).

Hyperglycemia

Hyperglycemia usually manifests in form of abnormal glucose tolerance test (GTT)(4) and can occur even within a few hours of steroid therapy. Steroid induced frank diabetes mellitus is rare (<1%), and develops in those who are probably predisposed to develop it. These include subjects with obesity and those with a first degree relative suffering from diabetes. Therefore, glucose level needs to be monitored more closely in these patients, or in those on concomitant GH therapy(5).

Hypothalamo-Pituitary-Adrenal Axis (HPA) Suppression

Adrenal suppression resulting from exogenous administration of glucocorticoids is by far the commonest cause of hypo-adrenalism in pediatric patients. Dose required to produce HPA suppression depends on:

- (a) *time of steroid administration*: Morning dose produces less suppression;
- (b) *steroid preparation*: Long acting preparations produce more suppression;
- (c) *duration of therapy*: Longer the duration, more the suppression; and
- (d) *route of administration*: Suppression caused by parenteral route is more than that produced by oral or topical route, in that order. HPA axis suppression is also reported in patients on inhalation therapy despite mouth rinsing(6).

HPA suppression may occur after long term treatment even with subnormal doses, or after high dose administration for as little as 3 days(7). Thus, abrupt interruption of treatment can precipitate acute adrenal insufficiency. A similar situation may occur when there is

TABLE II—*Important Differentiating Features of Idiopathic and Iatrogenic Cushing's Syndrome(2)*

Features prominent in idiopathic form	Features common in both forms	Features prominent in iatrogenic form
Hypertension	Obesity	Avascular bone necrosis.
Hypokalemia	Psychosis	Cataract
Menstrual irregularity	Edema	Glaucoma
Hirsutism	Myopathy	Pseudotumor cerebri
Acne, Striae	Renal calculi	Pancreatitis
Purpura	Poor wound healing	Panniculitis

inter-current illness or stress while the patient is on steroid therapy, since the atrophic adrenal gland cannot meet the increased demand for cortisol(8). These patients should be monitored for features of adrenal crisis which include anorexia, fatigue, nausea, vomiting, fever, arthralgia, myalgia, orthostatic hypotension, and finally circulatory collapse.

Prevention of adrenal crisis can be achieved by doubling the daily steroid dose in case of minor stress like upper respiratory infection, low grade febrile illness, minor surgeries like dental procedures and minor trauma. In case of a major stress like severe infection, major surgery etc, cortisol hemisuccinate 1-2 mg/kg I.V. should be given(8). Return to maintenance therapy may be achieved over a week.

HPA suppression returns to normal in variable time in different patients, but it is very unlikely to last beyond 1 year of steroid withdrawal. Hence, one needs to watch out for features suggestive of defective endogenous steroid production especially in response to stress or acute illness, during the year following withdrawal of steroids. It is important to remember that normal cortisol levels don't indicate return of normal hypothalamic response to stress(9).

To avoid precipitation of adrenal crisis,

various protocols have been described for withdrawal of steroid therapy. Some of these are presented in *Table III*. After withdrawal of long-term steroid therapy, one should continue to assess the HPA axis recovery by performing rapid ACTH stimulation test at the interval of 1-2 months till complete recovery. This test involves assessment of increase in serum cortisol level following I/M injection of 250 μg of synthetic ACTH. A normal response manifested by elevation in plasma cortisol to above 20 $\mu\text{g}/\text{dL}$ or rise of $>7\mu\text{g}/\text{dL}$ over the basal level, indicates complete recovery of HPA axis. In recent time low dose (1 μg) ACTH stimulation test is gaining acceptance as a more sensitive and accurate alternative to the conventional high dose test to screen for HPA axis suppression. As long as recovery is incomplete, patient needs close monitoring during inter-current stress, illness or surgery. In general, one should maintain this preventive attitude for the whole year following cessation of long-term steroid therapy.

Growth Retardation

Long-term high dose glucocorticoid medication in children inevitably leads to growth failure and protein catabolism. The extent of growth failure depends upon the following factors:

TABLE III—Recommended Protocol for Withdrawal of Steroid Therapy(7,8)

1.	Therapy of duration <3 days Stop at once.
2.	Therapy of duration 3-10 days: Taper by reducing the daily dose by 30%, then change to single morning dose and subsequently to alternate day dose. Stop when the therapeutic dose reaches about half the physiological secretion rate.*
3.	Long term therapy: Options (a) Reduce the dose by 25% each week. (b) Taper as quickly as possible to 40 mg of cortisol (Equivalent to 10 mg of prednisolone), then reduce by 10% every month to stoppage point defined above. (c) Rapid decrements of 2-5 mg of prednisolone every 3-7 days to physiological doses*, then switch to single morning dose, 2-4 weeks later, taper to about half the physiological dose. Continue this dose till circulating cortisol levels are >10 µg/dL in morning before taking medication (To be checked at 1-2 monthly intervals).

*The physiological secretion rate of cortisol is 12 mg/m²/day.

(a) *Dose of steroid:* A dose of >7.5 mg/m²/day of prednisolone or its equivalent will suppress growth(10).

(b) *Frequency of dosing:* More with twice daily as compared to once daily administration. Growth suppression is lesser in alternate day therapy. However, a dose of 10-40 mg/m² of prednisolone even in alternate day therapy can produce growth suppression(11).

(c) *Route and time of administration:* Though systemic administration obviously has a more significant effect on growth, long term topical application can also cause growth suppression, specially if applied to the moist napkin area, from where the absorption is significantly high(12). Long-term use of inhalational steroids in asthma can also lead to growth suppression(13). The growth suppressive effect is more pronounced in patients with milder disease by virtue of higher dose of steroid reaching the distal airways from where they are absorbed without metabolism. Evening

doses produce much more depression of growth by altering the nocturnal GH release(14).

Thus, all patients on long-term steroids regardless of route of administration should have a growth monitoring by measurement of weight and length/height. Knemometry, if available, can be used to detect short-term growth accurately in a cooperative child above 4 years of the age. Vertebral growth arrest lines (zones of increased density corresponding to vertebral plates) may be present as residual radiological changes for years after recovery from Cushing's syndrome(15).

If growth retardation is observed, one should shift to minimum possible doses and add adjuvant therapy where possible. The risk of permanent stunting can be reduced if the steroids are withdrawn before the pubertal spurt.

Hypertension

Hypertension is more commonly observed in endogenous Cushing syndrome since most

therapeutic preparations of CS have little or no mineralocorticoid activity. The reported incidence of hypertension in patients on long-term steroid therapy varies between 10-40%. Significant increase in blood pressure is reported within 5 days of administration of cortisol in high doses(6). Thus, a baseline blood pressure should be recorded and periodic monitoring done in patients on high dose or long term steroids.

Gastrointestinal Effects

Gastrointestinal side-effects including peptic ulcer disease, gastric ulceration and gastric hemorrhage are seen in about 0.4% of the subjects on steroid therapy(17). Those on concomitant NSAIDS are more likely to develop these. Their incidence is dependent on both the dose and duration of the therapy. Steroid induced ulcers are often asymptomatic due to the anti-inflammatory properties of steroids. To a large extent, these can be prevented by advising the patients to avoid taking steroids on an empty stomach. The symptomatic patients respond readily to antacids and H2 antagonists.

Acute pancreatitis is another major complication, especially in children. In an autopsy series published by Oppenheimer, 40% of children with nephrotic syndrome on steroid therapy were found to have evidence of pancreatitis(8).

Ocular Complications

Steroids can induce a number of ocular changes including cataract, glaucoma, non-specific keratitis, papilledema due to pseudotumor cerebri, changes in composition of aqueous humour and vitreous humour and variations in sclera thickness. Of these, posterior subcapsular cataract and glaucoma are more commonly seen in children, the rest are rare.

Glaucoma

Glaucoma is seen mainly with topical, high dose inhaled or oral steroids. While approximately 30% of the patients on topical therapy may be affected, the incidence is much lower with systemic steroids. It is usually observed early (within a few weeks) after initiation of steroid therapy. However, with systemic steroids, it may supervene after several years of use(19). Occasionally, it may also be seen years after cessation of steroid therapy due to alteration in trabecular network resulting in obstruction to outflow of aqueous humour. However, this complication is more likely in those patients who are predisposed to increase in intra-ocular-pressure (IOP). These include subjects with genetic predisposition, type 1 diabetes, high myopia, connective tissue disease specially rheumatoid arthritis, and patients with a first degree relative with primary open angle glaucoma. In most patients the intra-ocular pressure decreases within 1-4 weeks of cessation of steroids. Occasionally, if steroids are used for more than 18 months, irreversible changes in IOP may occur. Therefore, subjects on long-term steroids should have a six monthly IOP monitoring. Since the IOP-has a circadian rhythm which parallels cortisol circadian rhythm by a lag of 3 hr, the IOP should be measured preferably after 3 hours of steroid administration. The monitoring should continue even after the steroids are stopped.

Cataract

Cataracts are reported to occur in 11-38% of patients(20). Children may develop it with much lower doses of CS as compared to adults. Poor inhalation techniques while using inhalational steroids may directly expose the eye and lead to cataract formation. Steroid induced cataracts may range in severity from occasional subcapsular opacity or vacuoles in

the central region of the lens, to extensive opacities forming plaque on the back of the lens and extending forward into the cortex(21). While the less severe forms do not cause significant decrease in visual acuity and need to be identified by slit lamp examination, higher grades cause reduction in vision and can be detected by clinical ophthalmoscope. Cataract development is not related to total dose of steroid, duration of therapy or mean daily dose of steroids. It may be seen as early as within 6 months of the treatment, and even in alternate day therapy. Stopping treatment will halt the progress of cataract but will usually not reverse the changes already present. Hence, visual acuity assessment and ophthalmoscopy needs to be done 6 monthly in patients on steroid therapy(21). Direct exposure of vapors to the face should be avoided during inhalation by use of glasses, better design of inhaler or by the use of spacer.

Musculo-skeletal Effects

Osteoporosis

Osteoporosis, sometimes even leading to spontaneous fractures, is the most common serious adverse effect of steroid therapy encountered in 30-50% of patients(22). Prednisolone in the dose of 7.5 mg/day for 6 months more, or a cumulative dose of >10 g leads to bone loss(23). Children with their rapid bone turnover are particularly susceptible to develop symptomatic osteopenia from steroid therapy. The adolescents are also at a high risk since CS, by inhibiting bone formation, may prevent the subject from reaching his peak bone mass.

The bone loss predominantly occurs in trabecular bones. Therefore, more severe osteopenia is seen in vertebrae and ribs. The bone loss is partially reversible, as demonstrated by recovery of up to 20% of bone

density after the successful treatment of Cushing syndrome. Though several biochemical parameters are identified as markers of bone resorption and formation, they are difficult to assess in clinical settings. Conventional radiography detects osteoporosis in vertical and horizontal trabeculae. Pseudocallus formation is highly specific for steroid induced damages. However, bone densitometry utilizing dual energy X-ray absorption (DEXA) is the best investigation for early detection of osteopenia and is recommended annually for patients on long-term steroids. In addition, they should also receive prophylactic calcium and vitamin D supplements. The recommended daily dose of calcium is 800, 1200 and 1500 mg in the age groups of 1-5, 6-10 and 11-24 years respectively. Concomitantly, 400 IU of vitamin D should be administered daily(24). Exercise is a great stimulus of osteoblastic activity, hence regular age appropriate physical exercises should be recommended for these subjects.

Avascular necrosis of bone

Avascular bone necrosis usually occurs after about six months of CS therapy, but can manifest as late as 3 years after cessation of therapy. It is often bilateral and in >25% of the patients, involve only the hip. This is a dose dependent complication and once diagnosed, is irreversible and has no clearly satisfactory therapy. Any history of pain in hip or shoulder region in a child on steroid therapy should arouse suspicion of this possibility(25). Patients suffering from vasculitis, Raynauds phenomenon and those on cancer chemotherapy are at a high risk for this complication and should be closely observed. Bone scan should be performed for early detection. Once detected, efforts should be made to reduce the steroid dose to minimum possible and to consider using alternative therapy, if feasible.

Myopathy

Steroid myopathy is a slowly evolving, painless, proximal myopathy, which takes weeks to months to develop. It can occur in any age, though most commonly affected patients belong to 20-50 years age group. It involves sequentially, the pelvic girdle muscles, followed by shoulder girdle muscles and later, distal muscles.

The monitoring for this problem is difficult in situations where the primary disease itself produces muscle weakness (*e.g.*, polymyositis, SLE *etc.*). The distinguishing feature in steroid induced myopathy is occurrence of creatinuria in presence of normal muscle enzymes like CPK, aldolase, creatine kinase and aspartate aminotransferase. CT scan or iso-kinetic dynamic testing can also be used for its detection. Steroid myopathy is reversible with exercise(26).

Susceptibility to Infections

Infections are another major problem with long term CS therapy. Gram negative and fungal infections appear to be particularly prevalent(27). Re-activation of tuberculosis is of particular concern in countries with high prevalence of tuberculosis. Anti-tuberculous therapy should be given to those detected to have active infection and preventive prophylaxis offered to those with a positive tuberculin test.

Hepatitis B poses a special concern because steroids can aggravate chronic active hepatitis if associated with hepatitis B surface antigen positivity. Several other viral infections like varicella, herpes and CMV infections may complicate the course of CS therapy and follow a particularly virulent course. Candida and aspergillus infections have also been seen with chronic steroid therapy(28). Thus, vigilance for infections is

mandatory especially for patients on long-term therapy, since immunosuppressive action of steroids may also make the diagnosis difficult by modifying the clinical manifestations.

Neuro-psychiatric Effects

Emotional lability and psychological disturbances are not as common in children as in adults. Occasionally, change in school performance may be observed(29). Frank psychosis is rare in children. Steroids are also known to cause schizoaffective disorders, sleep disturbances, bulimia and other complications like pseudotumour cerebri.

Possible ways to minimize the steroid induced adverse effects

1. Use steroids only when indicated.
2. Use steroid for shortest possible duration of time.
3. Use low-potency steroid whenever possible.
4. Use topical/inhalational steroids, if possible.
5. Use adjunctive therapy, wherever possible. For example, in rheumatoid arthritis, physical exercise, anti-inflammatory agents and braces can help decrease dose and duration of steroid therapy. In cases of asthma, use steroid sparing strategies like reduction of allergens and smoke, treatment of associated rhinosinusitis or gastroesophageal reflux.
6. Prefer use of alternate day therapy as it causes lesser growth and HPA suppression. It also decreases chances of development of cushingoid facies, and improves carbohydrate tolerance and myopathy. However, alternate day therapy should always be employed with short acting steroids.

Key Messages

- Patients on long-term steroid therapy should be periodically monitored for complications.
- This includes a 3 monthly assessment of weight, height, blood pressure, 2 hours post prandial blood sugar and serum electrolytes. Six monthly ophthalmic evaluation and annual densitometry are also indicated.
- Vigilance should be maintained for inter-current infections since steroids modify their clinical manifestations.
- Dose of corticosteroids should be increased in presence of infections or other stress to avoid precipitation of adrenal crisis.

7. If low dose of steroids are required, give in morning in accordance with circadian rhythm to minimize HPA suppression.
8. Rinse mouth after use of inhalational steroids.

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