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Review

A Review On Adverse Effects Of Prolonged Steroid Use In Children

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Abstract

This review provides an overview of the impact of long-term use of steroids. Steroids are natural substances with many different effects in the human body, which begin over several days, as even birth control pills are a form of steroids. Natural steroids can be used to increase certain enzymes which a person's body may have trouble creating naturally, such as testosterone, which is vital in the growth and development. Although modern clinical management strategies have improved the outcome of paediatric patients with severe autoimmune and inflammatory diseases over recent decades, a proportion will experience ongoing or recurrent/relapsing disease activity despite multiple therapies often leading to irreversible organ damage, and compromised quality of life, growth/development and long-term survival. Several studies demonstrated that the use of alternate-day corticosteroid therapy maintains control of autoimmune diseases due to the prolongation of their therapeutic effect beyond their metabolic effect, with a significant decrease in side effects in patients. For this reason, the current recommendation for the use of these medications is in a short cycle to avoid adverse effects when used frequently and for prolonged periods of time. Patients on corticosteroid therapy, specially for a long period are likely to develop many adverse effects related to the therapy. The potency of dexamethasone and betamethasone in suppressing growth is nearly 18 times higher than that of prednisolone. There is some evidence that the administration of growth hormone can reverse these changes.

Keywords: Steroids, Hormones, Inflammation, Adverse effects, Corticosteroid side effects, Autoimmune disease, corticosteroids, Long term effects

INTRODUCTION

Autoimmune diseases are characterized by the loss of control in a T lymphocyte subgroup with alteration in the differentiation of the own and the foreign[(1)]. When a secondary activation of lymphocytes is associated with the production of antibodies against various antigens of the body, it is called humoral autoimmune disease and, in this case, the treatment involves providing drugs that stop the uncontrolled

production of autoantibodies to prevent the perpetuation of organ damage. The medications used for this purpose could trigger side effects that deteriorate the quality of life of patients and are usually dose dependent. Within these, the most used are systemic steroids. Several publications have been demonstrated that the use of alternate-day corticosteroid therapy maintains control of autoimmune diseases due to the prolongation of their therapeutic effect beyond their metabolic effect, with a significant decrease in side effects. It has been proven that steroid schemes on alternate days have a lower suppressive effect of the hypothalamic-pituitary-adrenal axis compared to treatment with daily intake when evaluated by means of insulin-induced hypo glycemia. There is also known that the steroid scheme on alternate days administered to children with nephrotic syndrome does not affect the expected growth for age. The concentration of the medication on alternate days maintains the serum levels and is associated with reduced suppression of the hypothalamic pituitary-adrenal axis[(17)]. The current recommendation for the use of systemic steroids is in short cycles and accompanied by other steroid-saving drugs to reduce the side effects of prolonged cycles. In this article, we presented the response observed in serum levels of autoantibodies in patients with autoimmune diseases treated with alternate-day corticosteroid therapy between January 2008 and January 2013 at the Clinical Immunology and Allergy Service of the National Medical Center 20 de Noviembre, ISSSTE, Mexico [(2)].

The etiology of the loss of normal self-tolerance in an autoimmune disease is considered multifactorial. Genetic, environmental, hormonal and immunological factors are all considered important in the development of these disorders. Nevertheless, the onset of at least 50% of autoimmune disorders has been attributed to unknown trigger factors. Physical and psychological stress has been implicated in the development of autoimmune disease, since numerous animal and human studies demonstrate the effect of sundry stressors on immune function. Many retrospective studies found that a high proportion (up to 80%) of patients report uncommon emotional stress before disease onset. Several studies suggest that stress is not only a participating factor, but can in fact cause disease exacerbation. Unfortunately, not only does stress cause disease, but the disease itself also causes significant stress in the patients, creating a vicious cycle. However, although physicians and patients agree that stress plays a role not only in the onset of many disease processes, but also in their exacerbation, there is very little clinical research work demonstrating the mechanisms by which this occurs. One of the reasons for this is that animal models are much easier to control environmentally, and that these models are genetically identical. In humans, factors like the environment, diet, and concomitant medication are difficult variables that need to be controlled [(3)].

Since their discovery in the 1940s, corticosteroids have become one of the most widely used and effective treatments for various inflammatory and autoimmune disorders. They are used as replacement therapy in adrenal insufficiency (at physiologic doses) as well as in supraphysiologic doses for the management of various dermatologic, ophthalmologic, rheumatologic, pulmonary, hematologic, and gastrointestinal (GI) disorders. In the field of respirology, systemic corticosteroids are used for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD) and severe, uncontrolled asthma, as well as for inflammatory parenchymal lung diseases such as hypersensitivity pneumonitis and immune mediated vasculitis.

These are just some of the many important uses of this group of medications that are utilized in almost all areas of medicine. Despite their beneficial effects, long-term systemic (oral or parenteral) use of these agents is associated with well known adverse events (AEs) including: osteoporosis and fractures; adrenal suppression (AS); hyper glycemia and diabetes; cardiovascular disease (CVD) and dyslipidemia, dermatological and GI events; psychiatric disturbances; and immunosuppression. However, they cause numerous side effects on various body systems and are also one of the most misused medicines. In UK alone, it is estimated that more than 250,000 people are taking systemic steroids and at least 10% of all children require some form of glucocorticoids during their childhood[(4)]. Some of the indications of systemic glucocorticoids in pediatrics include rheumatoid arthritis, ulcerative colitis, asthma and Crohn's disease. In pediatric dermatology, long-term systemic steroids may be used for the treatment of erythroderma due to atopic eczema, pustular psoriasis, childhood pemphigus, chronic bullous dermatosis of childhood, systemic lupus erythematosus, pyoderma gangrenosum or complicated hemangiomas. The doses required in these situations are much higher than those given in replacement regimens used for Addison's disease. Children taking such pharmacological doses of systemic steroids need to be carefully monitored to minimize the adverse effects[(5)].

HOW STEROIDS WORK

Steroids are synthetic versions of hormones produced naturally by the adrenal glands, which are two tiny glands located above the kidneys. Steroids reduce redness and swelling when taken in higher doses than your body generates naturally (inflammation). Inflammatory disorders like asthma and eczema can benefit from this. Steroids also lower the immune system's functioning, which is the body's natural defence against disease and infection. This can aid in the treatment of autoimmune diseases such as rheumatoid arthritis and lupus, which are caused by the immune system attacking the body incorrectly.

SIDE EFFECTS OF STEROIDS

When administered for a short period of time or at a low dose, steroids rarely cause significant side effect. However, they can sometimes have adverse effects include increased appetite, mood swings, and difficulty sleeping. When it comes to steroid tablets, this is the most prevalent occurrence. The side effects will normally go away once you've completed your therapy, but don't stop taking your drug without consulting your doctor first. Stopping a prescription medication can result in even more unpleasant side effects (withdrawal symptoms).

EFFECTS ON LONG TERM USE

Adrenal suppression is caused by long-term use of corticosteroids, which can blunt or inhibit the natural adrenal response to physiologic stress. Many cancer patients may get occasional doses of steroids as an antiemetic to prevent hypersensitive reactions or as adjuvants for pain control in order to avoid this impact. In 14 patients receiving high-dose prednisone for emesis prophylaxis prior to chemotherapy, Spiegel and colleagues performed Adreno Corticotropic Hormone (ACTH) stimulation assays. At 24 hours, 13 patients' adrenal function was suppressed, and 5 patients' adrenal function remained suppressed for more than a week. ACTH stimulation tests were done in nine women with ovarian cancer before and during chemotherapy in which dexamethasone was used as a pre-medication. A total of 523 medications were used. They observed effects on the hypothalamic-pituitary axis for up to eight days, but no long-term suppression was documented. Although adrenal suppression should be considered when patients who have had such treatment appear with hypotension and severe sickness, tapering steroids is probably not essential when they are given in brief, intermittent doses. Lefor, recently studied the use of replacement-dose steroids in cancer patients who are having surgery. The dangers of corticosteroid use in advanced cancer patients have been thoroughly investigated. Dyspepsia, peptic ulcer disease, sleeplessness, oral and vaginal candidiasis, anxiety, and glucose intolerance are among the acute adverse effects. Cushingoid look, weight gain, oedema, cataracts, osteoporosis, proximal myopathy, thinning of the skin, infection, and delayed wound healing are among side effects of long-term use. Corticosteroids can cause depression, agitation, and psychosis, among other neuropsychiatric side effects. As a result, it's critical to carefully assess the possible benefits of corticosteroid medication against the risks of side effects, as well as to continuously monitor the drug's efficacy. If there is no progress, the treatment should be changed or stopped[(6)].

CHOICE OF CORTICOSTEROID

Corticosteroids have two groups of actions: glucocorticoid effects (metabolic changes, anti-inflammatory effects) and mineralocorticoid effects (retention of salt and water, loss of potassium and hydrogen). Hydrocortisone is short-acting and is used orally for replacement therapy in adrenal insufficiency (in combination with fludrocortisone). Hydrocortisone sodium succinate, the water-soluble derivative, is administered parenterally for a quicker effect in emergencies. Prednisolone is widely used orally in the acute and long-term management of various disorders and for anti-inflammatory and immunosuppressant effects. Prednisone is a prodrug, converted in normal circumstances in the body to prednisolone.

Methylprednisolone has even less mineralocorticoid activity than prednisone / prednisolone while having a similar duration of action and may be preferred when mineralocorticoid effect is particularly undesirable. An alternate day regimen should be considered during long-term therapy.

Dexamethasone is highly potent, long-acting, with minimal mineralocorticoid activity and is used most often in the management of acute disorders. It is not suitable for alternate day regimens where the aim is to maintain the responsiveness of the hypothalamic-pituitary- adrenal (HPA) axis. Prolonged treatment is associated with severe suppression of the HPA axis; hence, it should generally be reserved for short-term management of specific indications. Betamethasone, similar to dexamethasone, is unsuitable for long-term alternate-day therapy due to its long duration of action. Alternative forms of glucocorticoids such as deflazacort, an oxazolone derivative of prednisolone, appear to have fewer effects on growth and corticosteroid-induced osteoporosis, but are not used in common practice.([7])

IMPORTANT ADVERSE EFFECTS OF CORTICOSTEROIDS

1. Endocrine/metabolic,
(a) Iatrogenic Cushings 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

RISKS OF STEROID SIDE EFFECTS

The risk of side effects depends on the
1. Dose: low dose (< 10 mg/day of prednisone), medium dose (10-20 mg/day), high dose (> 20 mg/day).
2. Type of steroid: (long-acting or short-acting)
3. Length of treatment: (Long-term treatment > 3 months)
4. Other medical problems

Fluid and electrolyte balance

The effect of gluco corticosteroids on fluid and electrolytes is due to their mineralocorticoid effect. This causes salt and water retention leading to edema, weight gain and hypertension. The potassium loss leading to hypokalemia can cause severe weakness. A diet low in sodium and rich in potassium should be followed and very rarely, potassium supplements may be required in children. Monitoring blood pressure at each visit is important, however, anti- hypertensives are rarely required in children. Fluid and electrolyte problems may be more dangerous in patients with associated cardiac illness.

Metabolic disturbances

Corticosteroids affect all metabolic pathways in the body. There is a 10-20% increase in blood sugar levels, mainly due to neoglucogenesis and reduced sensitivity to insulin. If the pancreatic function is normal, generally, diabetes does not develop. In children, it is essential to check blood sugar every six months or when there is development of persistent oral thrush. Frank diabetes is rare in children and is reversible and requires only slight modifications in diet. Hypoglycemic agents are not required in children. Neoglucogenesis leads to protein breakdown in muscle, skin and bone leading to delayed wound healing, skin and muscle atrophy. Reduction of collagen in tissues makes them fragile. This particularly affects the skin, membranes, capillaries and bone.

Growth suppression

Corticosteroids inhibit linear growth. The mechanism of this effect is unknown but may involve a combination of reduced growth hormone production and a direct inhibitory effect on bone and connective tissue. Growth suppression is more likely if steroids are given for more than six months. Apparent slow growth may be more due to a delayed puberty than actual side effects of the corticosteroids. It is important to monitor growth in children undergoing steroid therapy using growth charts. Unlike the other side effects of steroids, growth suppression is relieved by alternate day treatment. Doses of prednisolone ≤ 10-15 mg given on alternate days, do not slow down growth velocity significantly. However, this may not be effective in control of some of the inflammatory conditions. The potency of dexamethasone in suppressing growth is 18 times higher than that of prednisolone. There is some evidence that the administration of growth hormone can reverse these changes. Administration of deflazacort (oxazoline derivative of prednisolone), an alternative form of prednisolone, appears to have fewer effects on growth and corticosteroid-induced osteoporosis, but is not being commonly used. It is also important to rule out malnutrition as a cause of poor growth [(8)].

Growth retardation

Long-term high dose glucocoroticoid medication in children inevitably leads to growth failure and protein catabolism. The extent of growth failure depends upon the following factors:
(a) Dose of steroid: A dose of >7.5 mg/m2 /day of prednisolone or its equivalent will suppress growth.
(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.

(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. Long term use of inhalational steroids in asthma can also lead to growth suppression. 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. Thus, all patients on long-term steroids regardless of route of administration should have a growth monitoring by measurement of weight and length/height. Knemometery, 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. 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. 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. 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 Oppenhiemer, 40% of children with nephrotic syndrome on steroid therapy were found to have evidence of pancreatitis.

Ocular Complications

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

Cataract

Cataracts are reported to occur in 11-38% of patients. 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. 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. Direct exposure of vapours to the face should be avoided during inhalation by use of glasses, better design of inhaler or by the use of spacer.

Susceptibility to Infections

Infections are another major problem with long term CS therapy. Gram negative and fungal infections appear to be particularly prevalent. 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. 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.[9]

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. Frank psychosis is rare in children. Steroids are also known to cause schizoaffective disorders, sleep disturbances, bulimia and other complications like pseudo tumour cerebri [10].

POSSIBLE WAYS TO MINIMIZE THE ADVERSE EFFECTS OF STEROIDS

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.
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.

- 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 [11].

CONCLUSION

Our research underlined the need for greater information on patients who are on long-term corticosteroid medication. Patients have expressed a desire for more dependable, accessible, recurrent, individually-adapted, and unbiased information in their own words. Various tools have been offered, with a similar emphasis on the relevance of the physician's oral information. Written information with unfettered access is offered as a tool, even if it is geographically remote. Educational brochures or a web page (the most commonly utilised information media) were proposed in this scenario. To ensure its reliability and neutrality, this information should also be supplied in a medical structure. Finally, a treatment support group could complement the information provided by physicians by allowing patients to discuss about their difficulties with others who have similar experiences with corticosteroid therapy and providing a forum for the exchange of practical tools that improve quality of life. On follow-up, each child should be clinically evaluated for vital parameters, peripheral perfusion, weight, height, waist measurements and assessment for infections. Investigations which may be needed include blood sugar, electrolytes and a complete hemogram. Ophthalmic evaluation and densitometry may be needed every 6-12 months. Glucocorticoids, although potent and generally effective in many inflammatory and immunological conditions, are not without risks for producing serious side effects, especially when used in high doses for prolonged durations. The chance of significant side effects increases with the doseand duration of treatment and so only the minimum dose necessary to control the disease should be given. Measures for prevention and early recognition of glucocorticoid-induced adverse effects are important for better patient outcome.

REFERENCES

1. M. Cohn, “On the opposing views of the self-nonself discrimination by the immune system,” Immunology & Cell Biology, vol. 87, no. 2, pp. 113–119, 2009.

2. P. Sawla, A. Hossain, B. H. Hahn, and R. P. Singh, "Regulatory t cells in systemic lupus erythematosus (SLE); Role of peptide tolerance," Autoimmunity Reviews, 2012; 11(9); pp. 611–614.
3. P. Invernizzi and M. E. Gershwin, "the genetics of human autoimmune disease," Journal of Autoimmunity, vol. 33, no. 3- 4, pp. 290–299, 2009.
4. R. S. McHugh and E. M. Shevach, "the role of suppressor t cells in regulation of immune responses," Journal of Allergy and Clinical Immunology, vol. 110, no. 5, pp. 693–702, 2002.
5. A. V. Miller and S. K. M. Ranatunga, "Immunotherapies in rheumatologic disorders," Medical Clinics of North America, vol. 96, no. 3, pp. 475–496, 2012.
6. A. P. Grammatikos and G. C. Tsokos, "Immunodeficiency and autoimmunity: lessons from systemic lupus erythematosus," Trends in Molecular Medicine, vol. 18, no. 2, pp. 101–108, 2012.
7. C. Yildirim-Toruner and B. Diamond, "Current and novel therapeutics in the treatment of systemic lupus erythematosus," Journal of Allergy and Clinical Immunology, vol. 127, no. 2, pp. 303–312, 2011
8. C. M. Spies, C. Strehl, M. C. Van Der Goes, J. W. J. Bijlsma, and F. Buttgereit, "Glucocorticoids," Best Practice & Research Clinical Rheumatology, vol. 25, no. 6, pp. 891– 900, 2011.
9. E. Sarnes, L. Crofford, M. Watson, G. Dennis, H. Kan, and D. Bass, Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review, Clinical, therapeutics, vol. 33, no. 10, pp. 1413–1432, 2011.
10. A. K. McDonough, J. R. Curtis, and K. G. Saag, The epidemiology of glucocorticoid- associated adverse events, Current Opinion in Rheumatology, vol. 20, no. 2, pp. 131–137, 2008.
11. D. M. Poetker and D. D. Reh, "A comprehensive review of the adverse effects of systemic corticosteroids," Otolaryngologic Clinics of North America, vol. 43, no. 4, pp. 753–768, 2010.