

Management issues with exogenous steroid therapy

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ABSTRACT

Glucocorticoids (GCs) are extensively used for various inflammatory and autoimmune disorders, but long term use of these agents is not without complications. Almost every GC formulations (e.g. oral, topical, inhaled, etc.) can cause systemic side effects. It can range from minor side effects (e.g. weight gain) to life-threatening effects (e.g. adrenal suppression, sepsis, etc.), which may require immediate intervention. Therefore, the decision to institute steroid therapy always requires careful consideration of the relative risk and benefit in each patient. The objectives of this study are to discuss monitoring of patients on GCs and management of the complications of GCs.

Key words: Adrenal suppression, avascular necrosis, exogenous cushing's syndrome, glucocorticoids-induced osteoporosis

INTRODUCTION

Glucocorticoids (GCs) are useful in many disorders, and almost all the side effects of GC therapy are well known. Many of these side effects are preventable or curable. Hence, proper monitoring and management are of paramount importance. Simple general measures like those mentioned below may avoid development of the adverse events as much as possible.

GENERAL MEASURES

Dose and duration of GC therapy should be kept as low as possible. Pulse GC therapy should be used only when absolutely indicated. GC sparing agents should be used whenever possible. Short-acting GCs (e.g. hydrocortisone) are preferred for replacement therapy in adrenal insufficiency. Use of highly potent and long-acting GCs (e.g. dexamethasone) should be restricted to acute settings only and it should be avoided when long-term GC therapy is indicated. If at all required, prednisolone is

preferred for long-term management. Patient education and regular monitoring as advocated below are important in detection of these adverse effects as early as possible.

SPECIFIC MEASURES

Musculoskeletal system

Osteoporosis and fractures

GCs causes osteoporosis by both direct and indirect effects (e.g, suppression of gonadal steroids and GH-IGF1 axis, interference with the absorption of calcium, etc.) on the skeleton. It suppresses the bone formation, which is a central feature in the pathogenesis of GC-induced osteoporosis (GIO). GCs increases bone resorption by osteoclasts.^[1] Therefore, a rapid decline in bone mineral density (BMD) begins within the first 3 months of GCs use and peaks at 6 months, followed by a slower, steady loss with continued use. An increased risk of both vertebral and nonvertebral fractures has been reported with dosages of prednisolone as low as 2.5 mg daily.^[2] Vertebral fractures associated with GC therapy are often asymptomatic.^[3] Lateral spine x-ray can be done to look for asymptomatic vertebral fractures, especially in elderly patients.

Management

BMD should be done at baseline and then annually along with height measurement. BMD alone may not be able to predict the risk of fractures in patients receiving GCs, because fracture may occur independently of a decline in BMD.^[4] Because of this fact, American

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College of Rheumatology (ACR) Expert Advisory Panel recommends stratifying the patients using the FRAX calculator (developed by WHO) into low risk (10-year risk of a major osteoporotic fracture of < 10%), medium risk (10-20%) or high risk (>20% or a $T \leq 2.5$ or a history of a fragility fracture), and to decide about management according to the risk category for postmenopausal women and men age > 50 years.^[5] Use of FRAX is not appropriate in premenopausal women or in men younger than 50 years.

Low risk

If GC use is expected to last or has already lasted at least 3 months and the dose is 7.5 mg/day of prednisolone or higher, treatment with bisphosphonates is recommended.

Medium risk

If GC use is anticipated to last or has lasted at least 3 months and/or the dose is 7.5 mg/day or higher, bisphosphonates is recommended.

High risk

Treatment with bisphosphonates is recommended regardless of dose and duration of GC.

Premenopausal women

Treatment with bisphosphonates is recommended only in patients with fragility fracture according to dose and duration of GC.

In men younger than 50 years and premenopausal women who have not had a previous fracture, pediatric patients, and patients on inhaled steroids, treatment with bisphosphonates should be individualized due to the lack of sufficient evidence to recommend treatment in such a group of patients.^[5]

Bisphosphonates improve BMD and decrease the risk of vertebral fractures in patients treated with GCs.^[6] Teriparatide is more effective in the management of GIO with increases in BMD compared to alendronate.^[7] Calcium intake of 1,200-1,500 mg/day and vitamin D supplementation of 800-1,000 IU/day are recommended to every patient on GCs regardless of dose and duration of treatment.^[5] General measures such as weight-bearing activities, smoking cessation, avoidance of excessive alcohol intake (less than two drinks per day), and nutritional counseling are equally important in prevention of GIO. Denosumab is approved for treatment of postmenopausal osteoporosis. In future, it may become a useful agent in the management of GIO.

Osteonecrosis

GC therapy is the most common nontraumatic cause of osteonecrosis. It can occur even in the absence of GIO.^[8]

Although the risk appears to increase with higher doses and prolonged treatment, it may also occur with low doses or after short-term GC exposure. GC-induced avascular necrosis (AVN) tends to affect multiple joints. Hip and knee are the most common sites of involvement.^[8,9] Magnetic resonance imaging (MRI) is the most sensitive modality for diagnosis of osteonecrosis. Bone scan has the advantage of detecting AVN at the multiple sites and in the early stages, but it is less specific.^[10]

Management

At present, there is no consensus to recommend universal screening for asymptomatic AVN in long-term users of GCs. Physicians should have a high index of suspicion for persistent pain at typical sites after commencement of GCs. Conservative management includes bed rest and reduction of weight bearing. At present, there is not enough evidence to support the routine use of bisphosphonates in GC-induced AVN. Joint preserving surgeries (e.g, core decompression, osteotomy, bone graft, etc.) can be done in early stages of AVN. Usually, advanced stages of AVN requires arthroplasty.^[10] Therefore, early diagnosis is the cornerstone in the management of AVN.

Myopathy

Corticosteroids have direct catabolic effects on skeletal muscles leading to proximal muscle weakness because of type 2 muscle fiber atrophy. Diagnosis is mostly based on the clinical judgment. Muscle enzymes are rarely increased, electrophysiological analyses demonstrate unspecific and variable abnormalities. Therefore, it is difficult to make a diagnosis of GC-induced myopathy.^[11] Myopathy generally develops over several weeks to months of GC use. However with higher GC dose myopathy may develop more rapidly. Critically ill patients requiring large doses of GCs and neuromuscular blocking agents may develop critical illness myopathy.^[12] Myopathy may increase the risk of fall and subsequent fractures, especially in elderly patients. Concurrent use of some drugs (e.g statins) may aggravate myopathy in patients who are on GCs. GC-induced myopathy may lead to increase in perioperative morbidity and may prolong ICU stay. Symptoms generally improve within 3-4 weeks of dose reductions, and usually resolve after discontinuation of GC therapy. Muscle-strengthening exercise may help attenuate GC-induced muscle atrophy, but no specific treatment available at present.^[11]

Endocrine system

Hyperglycemia

GCs are the most common cause of drug-induced diabetes. In addition, GC-induced hyperglycemia increases the risk of infection. The effects of GC administration on glucose levels are observed within few hours of GC dosage and

appear to be dose-dependent. Postprandial glucose is more commonly deranged compared to fasting glucose levels.^[13] Fasting hyperglycemia can be seen in patients receiving higher once-daily GC doses or twice-daily dosing or with dexamethasone. While tapering GCs, fasting glucose normalizes well before postprandial.^[14]

Management

All patients should be educated about the classic signs and symptoms of hyperglycemia, so that they can be screened for GCs-induced diabetes whenever symptoms arise. The 2013 Canadian Diabetes Association (CDA) guidelines recommend that glycemic parameters should be monitored for at least 48 hours after initiation of GC therapy.^[15] Guidelines for blood glucose monitoring post-transplant suggest weekly monitoring for 4 weeks after transplant, at 3 and 6 months post-transplant and annually thereafter, as hyperglycemia after transplant has been shown to compromise graft functioning and survival.^[16]

Glycemic targets for patients with GC-induced diabetes should be individualized, but for most patients, fasting glucose and 2-h postprandial glucose targets of 4-7 and 5-10 mmol/L, respectively, are recommended.^[15] Sugar levels should be checked frequently whenever these targets are not met. If targets are not met with dietary and lifestyle modifications, pharmacotherapy is recommended. If blood glucose levels are <15 mmol/L, then glucose control can be achieved with oral hypoglycemic agents. If blood glucose levels are >15 mmol/L, then insulin is usually required to achieve glycemic control. In the absence of a contraindication, metformin is often recommended in combination with insulin. If fasting glucose is unaffected, then it is better to avoid long-acting insulin and long-acting oral hypoglycemic agents. If fasting blood glucose is also elevated, then both of them can be used. Short-acting insulin can be used at mealtimes.

Adrenal suppression and GC withdrawal syndrome

Withdrawal from chronic GC therapy presents significant challenges. These include the possibility of adrenal insufficiency after discontinuation of steroid therapy, recurrence of underlying disease as the GC is being withdrawn, and the possibility of steroid withdrawal symptoms.

AS often occurs following abrupt discontinuation of GC therapy. Endogenous cortisol production in a patient taking supraphysiological doses of exogenous GCs (more than 30 mg hydrocortisone per day or its equivalent) may be suppressed. Local GCs (e.g., inhaled GCs) may also be absorbed systemically to the degree that they can cause AS.^[17] Longer-acting GCs are associated with a higher risk of AS. Timing of GC administration may

also influence the development of AS, with morning administration being potentially less suppressive than evening doses. Alternate-day therapy is thought to be less suppressive than daily GCs based on the physiology of the hypothalamic-pituitary-adrenal (HPA) axis;^[14] however, further clinical evidence is required to prove it. Although there are no evidence-based guidelines for tapering of GCs, gradual GC tapering is frequently a part of treatment protocols to reduce the risk of relapse. Recovery of endogenous cortisol production is expected after stopping the exogenous GCs, though the time to recovery can vary.

If AS is suspected, early morning cortisol should be measured (with the prerequisite that GC dose is tapered to physiologic dose prior to test and no oral GC is given in the evening and morning prior to the test). If early morning cortisol <85 nmol/L, diagnosis of AS is confirmed. If morning cortisol is >85 nmol/L, but patient has symptoms of AS, low-dose (1 mcg) ACTH stimulation test should be performed to confirm the diagnosis. If peak cortisol (at 15-20 and 30 min) is <500 nmol/L, patient is likely to have AS.^[18]

Steroid withdrawal syndrome is characterized by lethargy, malaise, anorexia, myalgias, headache, fever, and desquamation of the skin. This syndrome is rare, and the exact etiology is unknown. Patients who have this syndrome have a normal HPA axis, and, therefore, are not suffering from adrenal insufficiency.^[19] Therefore, the choice of whether to continue replacement doses of steroids must be individualized.

Management

Possibility of AS should be kept in mind for any patients receiving supraphysiological GC doses for >2 weeks, multiple courses of oral steroids totaling >3 weeks in the last 6 months, or in patients presenting with symptoms of AS.^[20] AS can be life threatening if treatment is delayed. Therefore in a patient who is suspected of having acute adrenal crisis, GC should be started without waiting for the biochemical diagnosis of AS. If possible, the GC should be administered once-daily in the morning. Currently, there are no evidence-based recommendations for management of AS. If high-dose GC therapy is no longer required, then GC doses can be reduced relatively quickly (2.5 mg every 3-4 days) from pharmacologic to physiologic doses. Gradual tapering of GC is advised when risk of disease relapse is a concern. Once the dose of GC is tapered to physiological dose, it should be maintained at the same dose for at least 1 week (preferably hydrocortisone, which has a shorter half-life). An assessment should be made to diagnose AS (as described above) before proceeding to further reduction in GC dose. If the HPA axis is suppressed, reevaluation for AS can be done at 4-6 weeks interval to look for recovery of the HPA axis

from suppression. Patients with AS should be given stress doses of GCs as and when required during periods of stress. They should wear a bracelet or anything which can point toward AS (so that GCs treatment can be started in case of an emergency). In addition, patients on drugs like rifampicin may require more than usual dosage of GC. Patients with AS should receive physiological doses of GC until the HPA axis is recovered from AS.^[20]

Exogenous Cushing's syndrome

The diagnosis of exogenous Cushing's syndrome is obvious in the setting of treatment with GC (including local GC therapy). This can be more difficult in patients who have been treated with herbal medicines which often contain GC. It is indicative of treatment with supraphysiological dosage for prolonged duration. These patients are more likely to have AS. Features of mineralocorticoid excess (hypertension and hypokalemia) and androgen excess are less common in patients having exogenous Cushing's syndrome compared with patients who have endogenous Cushing's syndrome. Glaucoma, cataract, and osteonecrosis are more common in exogenous Cushing's syndrome compared to endogenous Cushing's syndrome.^[19]

GC therapy can lead to thinning of skin, increased fragility, purpura and red striae, impairment of wound healing, immunosuppression, and increase risk of cardiovascular diseases.

Growth failure

Oral GC therapy in children has been associated with growth failure and reduced final height.^[21] The mechanism of this effect is unknown but some experts attribute it to the reduce growth hormone production and direct inhibitory effect on bone and connective tissue. The risk of growth failure depends on dose, duration, and potency of steroids. The potency of dexamethasone and betamethasone in suppressing growth has been shown to be nearly 18 times higher than that of prednisolone.^[18] Therefore, lower potency agents (e.g., hydrocortisone, prednisolone) should be used in children whenever possible. Some of the trials in the past have suggested that daflazacort (derivative of prednisolone) and alternate day GC therapy have less growth suppression. Further clinical evidence is required to prove it.^[22,23] Currently, we cannot recommend routine use of growth hormone in patients with GC-induced growth suppression due to lack of adequate evidence.

Hypertension, dyslipidemia, and cardiovascular events

GCs having higher mineralocorticoid activity (e.g., hydrocortisone, prednisolone) can cause salt and water retention leading to edema, weight gain, hypertension, and hypokalemia. However, GCs may increase the blood

pressure by some other mechanisms. A significant increase in BMI, systolic and diastolic BP, total and LDL cholesterol and carotid intima media thickness, and also a decrease in cross-sectional compliance (CSC) after 4 weeks of steroid therapy (oral prednisolone) have been described. However, all these parameters returned toward baseline, 2 weeks after stopping the drug.^[24] Therefore, regular monitoring of blood pressure and lipid profile is recommended in patients using GCs at high doses or for prolonged periods.

GC use is associated with hypertension, hyperglycemia, obesity, and dyslipidemia. All of these increase risk of CV events. Rarely, arrhythmias and sudden death have also been reported with pulse GC therapy in patients with underlying kidney or heart disease. Longer infusion times for pulse GC therapy should be considered in such patients.^[25]

Cataract and glaucoma

Ocular side effects are some of the most neglected side effects of GCs. GC use is typically associated with the development of posterior subcapsular cataract. It usually requires earlier surgical intervention, as it affects the vision more significantly than other types of cataract. Usually, it develops only when high dose GCs are given for a longer duration.^[26] Systemic GCs can cause a painless increase in intraocular pressure. It can cause permanent optic nerve atrophy and visual field defects if left untreated and GCs are not withdrawn. Thus, glaucoma is a more serious ocular complication of GC therapy as compared to cataract. Annual ophthalmological assessment is required in patients on GCs.

Gastrointestinal system

GC therapy has been associated with an increased risk of gastritis and peptic ulcer formation, particularly when used in combination with nonsteroidal anti-inflammatory drugs. Proton-pump inhibitors can be used in GC users at high-risk of developing these complications. GC use is also a risk factor for developing pancreatitis.^[27] Acute liver failure has also been described with very high dose (cumulative dose more than 12-16 g) pulse GC therapy.^[28] Therefore, whenever pulse GC therapy is planned, cumulative dose of 8 g is considered safe.

Infections

GCs increase the risk of invasive fungal and viral infections.^[29] Old age, associated comorbidities, and concomitant use of other immunosuppressive drugs increase the risk even further. GCs should be used with caution in such patients. GC users may not manifest signs and symptoms of infection as clearly as nonusers, due to anti-inflammatory activities of GC, making early recognition of infections very difficult. Reactivation of

latent tuberculosis is also a concern in patients on GCs, especially in developing countries like India.

Psychiatric disturbances

GC use can lead to a wide range of psychiatric and cognitive disturbances including memory impairment and psychosis. These effects can occur as early as 1 week after initiating GC therapy and appear to be dependent on dose and duration of therapy.^[30,31] The risk of these events can be decreased by modifying the timing of GC administration (e.g., a single morning dose) and/or with the use of sedatives. Most patients with psychiatric reactions due to GCs usually recover from these symptoms with dose reductions or upon cessation of therapy.

CONCLUSION

Physicians should be aware of the possibility that almost all forms of GC therapy can cause systemic side effects. Therefore, judicious use of GC is advisable. Dose and duration of GC therapy should be kept as low as possible. Alternate day regimens can be used whenever long-term therapy is planned, to maintain responsiveness of the HPA axis. Highly potent and long-acting GCs (e.g. dexamethasone) are unsuitable for long-term use. In addition, preventive measures should be taken whenever possible to avoid development of the side effects discussed above. Regular monitoring is required to detect these side effects as soon as possible.

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