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Glucocorticoids: Complications to Anticipate and Prevent

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Abstract

Glucocorticoids (GCs) are widely used for inflammatory and autoimmune diseases. Their mechanism of action is most commonly rooted in genomic effects that have both beneficial and adverse consequences. The purpose of this review is to discuss the potential complications and side effects that may occur with GC use. Many of these complications are related to the dose and duration of therapy used. Evidence-based preventative strategies are discussed. Many recommendations are based on expert opinion and not on strong evidence. A 54-year-old man presents with proximal upper and lower extremity weakness. There are no rashes. The antinuclear antibody is negative; the erythrocyte sedimentation rate and C reactive protein are 24 mm/h and 3 mg/dL, respectively. An electromyography displays myopathic motor unit potentials with fibrillation and a muscle biopsy confirms polymyositis. Prednisone of 60 mg/d is initiated. What are the risks associated with GC use? What other studies and interventions should occur in this patient starting long-term GC therapy?

Keywords

autoimmune diseases of the nervous system, rheumatology, clinical specialty, vasculitis, central nervous system, autoimmune diseases of the nervous system, myositis, neuromuscular diseases

Introduction

Glucocorticoids (GCs) are often the first-line therapy for autoimmune diseases including many neurological conditions (Figure 1). Their use is commonly associated with complications and comorbidities. These include both immediate and long-term complications that are often related to the dose and cumulative dose of GCs. Generally, low dose is considered up to 7.5 mg/d, medium dose is >7.5 mg and <30 mg/d, high dose is >30 mg but <100 mg/d, and very high dose is considered greater than 100 mg/d of prednisolone. A pulse is considered between 250 and 1000 mg/d for 1 to 3 days.[1] The following review will summarize the evidenced-based effects of GCs and discuss issues that should be addressed when starting a patient on long-term GC therapy.

Glucocorticoid Potency and Half-Life

Hydrocortisone and betamethasone are the weakest and strongest GC, respectively. Betamethasone and dexamethasone have long half-lives and adverse effects can occur after the GC has been discontinued. Table 1 describes the potency of the various GCs.

Mechanism of Action of GC

The GCs have inhibitory effects on B and T cells and phagocytes, having activity on both the innate and acquired immune systems and therefore having efficacy in a broad range of both autoimmune and autoinflammatory diseases. They act on cells by both genomic and nongenomic mechanisms. The dose determines which effects occur. There is activation of the cytosolic GC receptor (cGCR) by a classical genomic mechanism. This mechanism results in the suppression of proinflammatory molecules called *transrepression* and upregulation of many anti-inflammatory molecules called *transactivation*. Transrepression accounts for many of the desired GC effects, while transactivation is associated with many of the undesirable side effects. Genomic effects take hours to days as compared to the nongenomic effects that occur rapidly within seconds to minutes. Nongenomic effects include GC

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- multiple sclerosis and other demyelinating diseases of the central nervous system
- autoimmune encephalitis
- central nervous system vasculitis
- transverse myelitis
- neurosarcoidosis
- chronic inflammatory demyelinating neuropathy
- myasthenia gravis
- polymyositis and dermatomyositis
- Duchene's muscular dystrophy
- mononeuritis multiplex (usually secondary to vasculitis)

Figure 1. Neurologic diseases that may be treated with glucocorticoids.

Table 1. Glucocorticoid Dosing and Equivalency.

Generic Name	Brand Name	Dose Equivalent
Hydrocortisone		4 mg
Prednisone		1 mg
Prednisilone		1 mg
Methylprednisilone	Solumedrol	0.8 mg
Dexamethasone	Decadron	0.15 mg
Betamethasone	Celestone	0.12 mg

signaling through membrane associated receptors and second messengers.[2] The nongenomic effects[3] are far more significant at doses greater than 100 mg/d.

Adverse Effects

Weight Gain and Fat Redistribution

The GCs are associated with weight gain. This is probably the most common side effect in patients on chronic GCs.[4] In a study of rheumatoid arthritis, patients taking 5 to 10 mg/d over 2 years had an increase in mean body weight of 4% to 8%.[5] This is thought to be related to increased appetite and dyspepsia that is relieved with eating. Fat redistribution produces a cushingoid appearance including truncal obesity, a buffalo hump, enhanced supraclavicular fat pads, and moon facies in patients on moderate doses of prednisone for prolonged periods.

Osteoporosis and Fracture

Observational studies suggest that as many as 40% of patients on GCs will develop a fracture related to bone loss. The risk factors associated with GC-induced osteoporosis include older age (>60 years), low body mass index (<24 kg/m^2), having an underlying chronic inflammatory disease (ie, rheumatoid arthritis), certain GC receptor genotypes, increased 11β-hydroxysteroid dehydrogenase type 1 expression, higher GC dose, longer duration of therapy, and low bone mineral density. General risk factors for osteoporosis include both a personal and family history of fracture (hip fracture specifically), smoking, excessive alcohol consumption, and frequent falls.[6-8]

The mechanism of GC-induced osteoporosis appears to be related to the inhibitory effects on bone formation more than the effects on bone resorption. In a large part, this is due to the GC effects on the osteoblast lineage.[9,10] This is especially interesting in that the treatment of this condition is with agents such as bisphosphonates that prevent bone resorption. In a study comparing a bisphosphonate, alendronate, to teriparatide (an anabolic agent) in GC-induced osteoporosis, bone mineral density improved more in patients receiving teriparatide.[11] Of note, these patients were on average in their 50s and had a mean lumbar spine T score of −2.5; therefore, this should be viewed as secondary prevention of osteoporosis. The current guidelines still recommend bisphosphonates as the first-line agents for primary prevention of GC-induced osteoporosis.

The World Health Organization's fracture prevention algorithm (FRAX) underestimates the fracture risk in patients on GC therapy. The FRAX should therefore be used with caution in determining the probability of fracture in this group of patients. Though it takes into account GC use, it does not account for dose or duration of therapy. Prevalent fractures commonly occur in the vertebral spine, yet the FRAX uses the bone mineral density at the femoral neck.

In 2010, the American College of Rheumatology published a guideline for the prevention and treatment of GC-induced osteoporosis.[12] Based on this guideline, if a patient (postmenopausal woman or man older than 50 years) is at low risk (probability of fracture <10%) and on ≤7.5 mg/d, no pharmacologic intervention is recommended. If they are at medium or high risk (based on several variables plus the FRAX and probability of fracture >10%), pharmacologic intervention is recommended. If the patient is premenopausal or younger than the male group above, then pharmacologic intervention is recommended if there is a fragility fracture in a man or woman (of non-childbearing age). If the woman has a fragility fracture history and is of childbearing age, therapy is recommended only if GCs are to be prescribed for longer than 3 months.

Prevention of GC-induced osteoporosis should include adequate calcium and vitamin D (1500 mg calcium and 800 IU vitamin D per day, divided dose; level A evidence).[12,13] Weight-bearing exercise is important for bone remodeling. Alternate-day GC regimens have been studied but have not been shown to produce less bone loss than daily regimens.[14,15] Other recommendations that have been suggested but are based on level C evidence include smoking cessation, less than 2 alcoholic beverages per day, a baseline vitamin D 25-OH level, nutritional counseling on calcium and vitamin D intake, a fall risk assessment, a baseline bone densitometry, and assessment of fragility fractures.

Osteonecrosis

Osteonecrosis occurs in 5% to 40% of patients treated with GC. This often happens with higher doses and longer duration

of therapy but can happen with short-term exposure. It is more strongly associated with the peak dose of GC rather than the cumulative dose but seldom occurs on doses of less than 20 mg/d. Felson et al showed a 4.6-fold increase in the rate of osteonecrosis for every 10 mg/d increase in mean daily dose of prednisone in the first 6 months of therapy.[16] One should consider the diagnosis in patients with new joint pain (hip, knee, and shoulder are most commonly affected but can also affect ankle and spine) with movement, typically without swelling or warmth.

Ocular Complications

Cataracts are usually in the posterior subcapsular location and are differentiated from senile cataracts by often being bilateral and more progressive. There is some data to suggest this rarely occurs in patients on doses <10 mg/d or in those treated for less than 1 year.[17] Intraocular pressure can also increase with GCs but usually in response to GC eye drops and rarely from systemic GCs. When it does occur with systemic GCs, it usually occurs in patients already at risk. Central serous retinopathy can occur with either systemic or topical use of GCs. Edema can separate the retina from the choroid. Treatment is dose reduction of the GCs[18]

Hyperglycemia and Diabetes

In patients with known diabetes, hyperglycemia is more common in those on GCs. Patients with pre-diabetes may develop a hyperglycemic state when treated with GCs. Frank diabetes rarely occurs secondary to GCs. A fasting glucose should be checked on patients initiating GC therapy and one could consider the level of hemoglobin A1C to assess for a prediabetic state that might evolve to diabetes on GCs.[19,20]

Cardiovascular Effects

Ischemic heart disease and heart failure may be increased in patients on chronic GCs. In a population-based study, the rate ratio for heart failure, myocardial infarction, stroke, and transient ischemic attacks combined was 3.7, 3.3, 1.7, and 7.4, respectively.[21] Another study in patients exposed versus unexposed to GCs found no difference in cardiovascular events.[22] Most of these studies have been done in patients with rheumatic disease. It is difficult to control for disease activity in these patients, which may confound these outcomes.

Atrial fibrillation and flutter has also been reported to be increased in those on high-dose GCs, even when controlling for pulmonary or cardiovascular disease.[23–25] However, low-dose GCs appears to decrease the risk of arrhythmias as shown in patients that have undergone coronary artery bypass surgery.[26]

Some studies suggest that moderate or higher doses of prednisone promote fluid retention.[27] Other studies have not supported this association.[28,29] Hypertension has been described in association with GC use; however, this data might be confounded by rheumatoid arthritis patients who have more disease severity.[30] Observational studies suggest that lipid profiles are adversely affected by prednisone doses >10 mg/d; however, this has not been confirmed in a national US sample. Furthermore, other studies looking at moderate doses of GCs tapered over the course of 3 months did not adversely affect the lipoprotein levels.[31]

Infection

Glucocorticoids decrease the production of proinflammatory cytokines and effect phagocyte function, thereby increase the risk of infection. Signs of infection may be absent in the setting of GCs. There is a dose-dependent (>10 mg/d) and cumulative dose-dependent (>700 mg) risk of infection in those taking GCs.[32] Other factors such as the primary disease, disease activity, other immunosuppressive agents, the age of the patient, and functional status also affect this risk.[33] Common infections are still most common in this group of patients. This includes herpes viral infections, staphylococcus bacterial infections, and candida fungal infections. Strongyloides stercoralis can reactivate causing a severe and sometimes fatal hyperinfection. Opportunistic infections can occur in those on chronic GCs but usually in conjunction with other immunosuppressive agents. *Pneumocystis carinii pneumonitis* (PCP) can occur in the setting of GCs of short-term use at high doses or chronic use at moderate doses. However, this has been studied in the form of a systematic review, followed by a Cochrane review.[34,35] The results showed that PCP prophylaxis should be used when the risk of PCP is 3.5% or higher. Within the autoimmune diseases studied, only granulomatosis with polyangitis (formerly called Wegener granulomatosis) approximates this risk and should be treated. The only neurologic diseases included in these meta-analyses were the inflammatory myositides where the risk of PCP was 1.5% not meeting indication for prophylaxis. Many pulmonologists do treat patients with PCP prophylaxis in the setting of interstitial lung disease. It should be remembered that though myositis did not approximate a high enough risk for treatment, a significant proportion have interstitial lung disease.

The odds of developing tuberculosis (TB) in the setting of GCs are estimated to be 4 to 1. This data comes from the UK-based medical record system, where cases of TB were confirmed and controls were matched to several variables.[36] This risk is probably increased especially in patients with underlying pulmonary disease. Currently the Center for Disease Control does not recommend treatment of latent TB infection in patients on chronic GCs, because though they acknowledge that the risk is higher in these patients, they cannot state exactly the dose threshold and GC duration that increase the risk.[37] One should also consider that response to the tuberculin skin test will be dampened once a patient is on 15 mg or more per day of GCs for 2 to 4 weeks.

Response to vaccination is usually preserved in those on chronic low-to-moderate doses of GC, though there may be

an attenuated response on higher doses. Live vaccines are contraindicated on doses greater than 20 mg prednisone per day. It is recommended in patients who have been on high-dose GCs for 2 weeks or more that there is a 3-month waiting period after discontinuation of GCs before live vaccinations are given.[37]

Gastrointestinal Complications

There is little evidence that GC use increases the risk of peptic ulcer disease. However, in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) with GC, the risk of peptic ulcer disease is increased 4-fold as compared to a 2-fold risk of ulcer on NSAID alone. An initial association[38] was then discounted by meta-analyses.[39] In a nested case–control study, the increased risk was attributed to the addition of NSAIDs to GC therapy.[40] Therefore, antiulcerative therapy is not indicated in patients using GC, unless they are also taking NSAIDs.

Steroid-Induced Myopathy

This is a rare complication and occurs even more rarely with low doses of prednisone. It often presents with a proximal lower extremity weakness and a normal creatinine kinase. Electromyogram is usually normal. Histopathology shows loss of type IIa fibers. Muscle strength improves as the steroids are tapered.

Hypothalamic–Pituitary–Adrenal Axis Suppression

This occurs in relation to the dose and duration of GCs used. Most patients with autoimmune diseases requiring GCs will be suppressed because of the long duration of therapy and the relatively higher doses that are initially required. In general, patients receiving approximately 10 mg/d of prednisone for 3 weeks or more should be considered suppressed and should be given stress-dose steroids in the appropriate situation. Some argue that these patients should wear a medic alert bracelet and guidelines recommend an emergency medical information card be carried by patients on chronic GCs, though this is considered level IV evidence and based purely on expert opinion.[20] Tapering of GCs should be done slowly to allow recovery of the adrenal function. However, exactly how slowly is a matter of practice style and is not based on evidence. In general, between 60 mg and 20 mg, patients are tapered by 10 mg every 2 weeks. Between 20 mg and 10 mg, patients are tapered by 2.5 mg every 2 weeks and below 10 mg, patients are tapered by 1 mg per month.

Psychiatric Complications

Psychiatric manifestations associated with GC use are relatively common and range from mild anxiety and sleep disturbance to severe mood disorders, psychotic depression, and delirium.[41] Not surprisingly, manifestations tend to occur on higher doses. The most common symptom appears to be hypomania and mania.[42–47] Depression appears to increase with duration of GC therapy.[48–50] Cognitive dysfunction, especially involving declarative or verbal memory is well described[51–57] Though these manifestations often get better with tapering the steroids, pharmacologic intervention is often necessary to control symptoms. It should also be remembered, that because of the long half-life of dexamethasone and betamethasone, onset of symptoms can occur after the discontinuation of the GC.

- ✓ Counsel on weight bearing exercise, alcohol consumption <2 drinks per day, smoking cessation
- ✓ Consider baseline dual x-ray absorptiometry
- ✓ Consider baseline vitamin D-25OH
- ✓ Diabetes screen
- ✓ Calcium 1200-1500mg and vitamin D 800-1000IU per day (divided dose). If the patient is on a proton pump inhibitor, a calcium citrate formulation should be considered for calcium absorption
- ✓ Bisphosphonate therapy in the appropriate patient
- ✓ Vaccinations are up to date including live vaccinations if indicated
- ✓ Consider fall risk assessment

Figure 2. Considerations when initiating glucocorticoid therapy.

Summary

Glucocorticoids are effective drugs for many autoimmune diseases. However, there are serious adverse effects that can ensue. These are often dose related and related to the duration of therapy. Several of the complications occur in patients already at risk for these adverse events. Many of the more serious complications occur at doses greater than 20 mg of prednisone per day. Risk of complications should be discussed with patients and screening for these complications should be performed at baseline and intermittently in selected patients (Figure 2). Calcium, vitamin D, weight-bearing exercises, smoking cessation, and reduction in alcohol consumption (to <2 drinks per day) should be recommended in all patients on chronic GCs.

Declaration of Conflicting Interests

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