CHAPTER **14**

Adverse Events of Corticosteroids

Stephan J. LaPointe, DPM, PhD
Kelly S. Brennan, DPM

INTRODUCTION

The impetus for this article is personal. During my treatment for non-Hodgkin lymphoma, a part of each round of chemotherapy was 100 mg prednisone daily in 2 doses for 5 days every 3 weeks. The first round of chemotherapy was scheduled the same day we had scheduled ankle surgery. This was to be the second surgery on the same ankle. The first involved removal of a 2.5 cm osteochondral defect, bone harvesting from the tibia into the talar defect, and resurfacing of the talus with morselized pediatric cartilage. It was to be an attempt to save it in lieu of arthrodesis. The plan was subchondroplasty of the tibia and talus resurfacing of the talus again with pediatric cartilage. The surgery was canceled to treat the cancer. I was able to ride a bike everyday for 72 days during chemotherapy, and for weeks following without ankle symptoms for the first time in 4 years. In 8 days between Christmas and New Year's I rode 620 miles, two of those days were 125 miles. In private practice I do not prescribe long-term steroid therapy. However, I do use tapered dose packs on occasion for various acute conditions or for recalcitrant chronic conditions. As a patient I became curious about the possibility of using steroids more long-term for my ankle symptoms. To that end this was a review to weigh the risks and see if there was a prescribing approach to minimize them.

As part of the research for the paper I found the following article: "A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy." by Lieu et al 2013 (1). The following review is principally a synopsis of that paper with the addition of other content to supplement and bring it current to 2017.

CORTICOSTEROIDS

Corticosteroids are synthetic forms of naturally occurring steroids produced and secreted by the adrenal cortex. They can be divided into glucocorticoids (GCs) or mineralocorticoid activity. Mineralocorticoids influence kidney function and regulate water and electrolyte balance. A list of systemic corticosteroids, equivalent dosing, duration of action and therapeutic indications are found in Table 1.

Table 1. Equivalent steroid dosing.

Glucocorticoids	Approximate equivalent dose* (mg)	Duration of Action (hours)	General therapeutic indications
Short-acting			
Hydrocortisone	20	8-12	Relatively high mineralocorticoid activity makes it suitable for adrenal insufficiency
Cortisone	25	8-12	Similar to hydrocortisone
Intermediate-acting			
Prednisone	5	12-36	High glucocorticoid activity makes it useful for long-term treatment, and as an anti-inflammatory/immunosuppressant
Prednisilone	5	12-36	Similar to prednisone
Methylprednisolone	4	12-36	Anti-inflammatory/immunosuppressant
Triamcinolone	4	12-36	Anti-inflammatory/immunosuppressant
Long-acting			
Dexamethasone	0.75	36-72	Anti-inflammatory/immunosuppressant; used especially when water retention is undesirable due to its low mineralocorticoid activity Usually reserved for short-term use in severe, acute conditions given its high potency and long-term duration
Betamethasone	0.6	36-72	Similar to dexamethasone

Adapted from (ref. 52). *Equivalent dosing show is for oral or IV administration.

GCs have powerful anti-inflammatory, immunosuppressive, vasoconstrictive, and anti-proliferative properties. They are used to treat a variety of disorders across many medical disciplines. Rheumatology applications include rheumatoid arthritis, systemic lupus erythematosus (SLE), polymyalgia rheumatica, polymyositis rheumatica, polymyositis/dermatomyositis, polyarteritis, and vasculitis. Included respiratory or allergic conditions include asthma, chronic obstructive pulmonary disease, sarcoidosis, food and drug allergies, allergic rhinitis, pneumonia, interstitial lung disease, nasal polyps, urticaria/angioedema and anaphylaxis. Gastroenterology prescribes GCs for ulcerative colitis, Crohn's disease, and autoimmune hepatitis. Ophthalmology uses include uveitis and keratoconjunctivitis. Hematology conditions include lymphoma/leukemia, hemolytic anemia, and idiopathic thrombocytopenic purpura. Dermatology uses include pemphigus vulgaris, and contact dermatitis. Endocrinology uses include adrenal insufficiency and congenital adrenal hyperplasia. Other uses include multiple sclerosis, organ transplantation, nephrotic syndrome, hepatitis, and cerebral edema.

Although widely used, these agents are known to cause a significant number of adverse events or complications with long-term use. It is imperative that we understand these consequences and their symptoms for proper patient education, to identify the adverse effects and mitigate their sequelae, and for modification of our course of treatment when we prescribe or treat patients on steroids. Adverse events include increased risk of infections, osteoporosis, aseptic necrosis and higher fracture risk, decreased wound healing and skin lesions, hyperglycemia and steroid induced diabetes, weight gain or Cushingoid adipose changes, gastric ulcers, and bleeding, glaucoma and cataracts, hypertension and fluid retention, insomnia and mood disorders. Lastly, long-term use can cause decreased stress response or suppression of the hypothalamic–pituitary–adrenal (HPA) axis. These consequences, whether they are dose dependent, their symptoms and how to mitigate or treat them will be discussed.

Please be cognizant that although adverse events are dose and duration dependent there has not been established thresholds for adverse events. It should also be noted that pharmacologic doses used in non-endocrine applications are supra-physiologic and are more likely to cause complications.

HPA AXIS SUPPRESSION

The hypothalamus releases corticotropin releasing hormone that signals the pituitary to secrete adrenocorticotropic hormone (ACTH). The latter signal acts on the adrenal cortex to produce cortisol. Suppression of the HPA axis occurs when the adrenal cortex production of natural cortisol is suppressed due to external GCs. The length of treatment and dose are not good predictors of suppression (2). However, when treated less than 1 week the risks are low (3). Clinicians should suspect suppression and screen with biochemical testing in patients receiving greater than 2 consecutive weeks or more than 3 weeks of therapy in the last 6 months or if symptoms are present (4). The first step for suppression monitoring is testing of serum cortisol before 8 am followed by rapid adrenocorticotropic hormone stimulation test with cosyntropin. The details for suppression screening are listed in Ahmet et al (4). Although specificity is 100%, sensitivity is low at about 60%, so if suppression is suspected or symptoms are present referral to endocrinology for further testing is appropriate (5). The definitive test is the insulin tolerance test. However this test is complicated and risky so more often the low-dose adrenocorticotropic hormone (ACTH) test is performed (6-8).

HPA axis suppression can lead to the inability to respond to new stress or if GCs are abruptly discontinued can lead to symptoms of suppression. The symptoms of suppression include nausea, vomiting, weakness/fatigue, malaise, diarrhea, abdominal pain, headache, fever, weight loss, myalgia, arthralgia, psychiatric disorders, and stunted growth in children. Severe cases can result in an adrenal crisis that can lead to hypotension, decreased consciousness, lethargy, seizure, coma, hypoglycemia, and hyponatremia.

To lessen the risk of suppression, the lowest dose and duration of action should be administered (Table 1). GCs should be taken in the morning and when possible on alternate days or intermittently (9,10). The longer the therapy, the more likely suppression occurs. Tapering to hydrocortisone at physiologic doses is recommended before GCs are discontinued to avoid suppression symptoms and its complications. Biochemical testing should then be performed before discontinuing. If there is biochemical evidence of suppression, then it is safest to treat as though the patient is suppressed.

Stress dosing of patients on GCs started in 1952 after the first reported case of a patient that perished secondary to hypotension during an orthopedic procedure (11). A systematic review of the literature identified only 9 studies involving 315 patients to review (12). Of these there were 2 placebo controlled, double blinded random controlled trials (13,14). The first involved 18 patients receiving GCs who all had a suppressed HPA axis as defined by the cosyntropin stimulation test. It should be noted that no patient taking 5 mg of prednisone exhibited suppression even when taking it for years. The treatment group of 6 patients received cortisol and 12 received normal saline and all were taking at least 7.5 mg of prednisone. All continued their GC regimen leading up to and following surgery. Each group had 1 patient with hypotension that responded to volume replacement. There were no hemodynamic differences in heart rate or blood pressure between the 2 groups (13).

Table 2. Preoperative steroid dosing.

No supplemental steroids	Minor/intermediate intensity surgical procedures
	Prednisone (or equivalent) <= 10 mg daily
	Every other day steroids
	Topical steroids
Hydrocortisone 50 mg intraoperatively and q8h after surgery until tolerating po intake when the patient's usual dosage should be restarted	Major surgical procedures
	Volume refractory hypotension
	Patients require physiologic replacement therapy*

These recommendations are based on the assumption that patients will maintain their usual glucocorticoid dosing up until and including the day of surgery.

* Patient with primary adrenal failure (Addison's disease), congenital adrenal hyperplasia, secondary adrenal failure due to hypopituitarism.

The second study involved a double blinded crossover study of 20 organ transplant patients undergoing gingivectomy. Since all the patients were to undergo 2 surgeries, they each functioned as their own control. No blood pressure differences were reported (14). A subsequent Cochrane review also only located these 2 studies and could not support or refute the need for GC supplementation (15). Another study in 1968 of rheumatoid arthritis patients undergoing knee surgery examined both cortisol levels and blood pressure with 21 patients treated and 20 controls. Although the controls did have blunted cortisol levels there were not any differences in blood pressure (16,17).

Although Liu et al have outlined their recommendations for stress dosing for surgery, MacKenzie and Goodman refute this practice since objective data do not support it (Table 2) with few exceptions. Patients taking ≤10 mg of prednisone per day, on alternate day therapy, or using topicals have not been shown to require additional dosing regardless of the procedure assuming they will continue their current regimen. In major surgical procedures where this may be deemed necessary, physiologic dosing mirroring what is produced during the stress of surgery about 75 to 150 mg/day is recommended. They recommend 50 mg intravenous (IV) intraoperatively then every 8 hours for 48 to 72 hours until oral supplementation is tolerated.

BONE METABOLISM

Bone health complications of GC use include osteoporosis leading to increased fracture rates and aseptic necrosis. Early on in therapy, GCs produce an increased osteoclastic activity and after 6 months, a decrease in osteoblastic activity both decreasing bone mineral density (BMD) and increasing fracture risk (18–20). A large meta-analysis of over 80 studies in adults found significant decreases in BMD, leading to increased rate of fractures typically in the first 3 to 6 months of therapy when dosing is greater than 5 mg of prednisolone. This was independent of age, sex, or underlying disease process (21). Kanis et al looked at 42,500 subjects and found that prior or current use of GCs increased the risk of fracture regardless of BMD or prior fractures (18).

If GC therapy ≥5 mg of prednisone is to exceed 3 months, BMD should be assessed at baseline and after the first year of treatment. If BMD is stable after 1 year and fracture risk is low then it can be rechecked in 2 to 3 years. If bone density has declined after 1 year then both fracture risk and BMD should be checked annually. These guidelines are outlined in the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX; URL:www.sheffield.ac.uk/FRAX) (22-25). It is important to make adjustments of the FRAX tool for assessment depending on the GC dose and age as outlined by Kanis et al and Liu et al (1,26). The American College of Rheumatology recommends pharmacologic treatment of BMD in patients with low to medium risk of fracture (10 year fracture rate <20%) if ≥7.5 prednisone or equivalent for >3 months. All patients should be treated if fracture risk is high (10 year fracture rate >20%) even if not on GC protocol (23-25,27,28).

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) have joint published their guidelines on postmenopausal osteoporosis. They identify, as does the FRAX tool, the increased risks associated with GC therapy. Their algorithm includes prior fragility fractures, BMD and FRAX tool assessment followed by calcium/Vitamin D deficiency

correction, and pharmacological therapy. Drug holidays are also recommended to reduce the risks of atypical femur fractures and other risks with long-term drug therapy (29).

Pharmacological therapy first line treatment of osteoporosis includes the bisphosphonates alendronate, risedronate and zoledronic acid, and teriparatide (30-36). The AACE/ACE also include in their protocol denosumab and in certain cases ibandronate or raloxifene (29). Other recommendations include behavior modification including decreased alcohol, smoking cessation, weightbearing and strength training exercise, fall risk assessment, and calcium and vitamin D augmentation (23-25,27,28). Adults on high dose GC therapy should be taking 1,200 mg/day of calcium and 800 to 2,000 IU of vitamin D (23,25,29).

Osteonecrosis increases with dose and length of treatment, however, it may occur with lower doses or shorter treatment. It develops in 9-40% of patients on long-term therapy either administered orally or via intra-articular injections (37). A meta-analysis of long-term steroid use that included 57 studies and 23,561 patients found that high dose steroids resulted in up to 10 times higher rate of osteonecrosis. Patients taking >40 mg were at higher risk for a 3.6% increase in risk for every 10 mg increase in doses. The study does point out it is not possible to remove confounding factors such as the underlying disease process (38). One study found an increased risk of avascular necrosis with 2-3 14-day tapered dose packs (440 to 1,290 mg prednisone) with a relative risk of 6 (95% confidence interval [95% CI]1-43) within the prior 3 years. The same study did not find increased risk with a single dose pack (<430 mg prednisone) (39).

Another large population study of 24 million patients found 98,390 patients prescribed at a single methylprednisolone dose pack. Of these 130 developed osteonecrosis (0.132%, 95% CI 0.109-0.155%). One dose pack resulted in a RR of 1.597 (95% CI 1.339-1.843) compared to controls, which was statistically significant ($P < 0.001$). If patients had received more than 1 dose pack the percentage rose to 0.230% (95% CI 0.176-0.283%) with a RR of 2.763 (95% CI 2.186-3.341). This study illustrates that a single dose pack results in a low but statistically significant increase in osteonecrosis and this should be used to counsel patients (40).

Other risk factors for osteonecrosis include alcohol, hypercoagulable states, sickle cell anemia, radiation therapy and HIV infection (41). Of 269 patients (270 patients studied) in 1 study of patients that had pain with femoral head osteonecrosis all occurred within 3 years with a median of 18 months (42). Children treated for some forms of leukemia and lymphoma are also at risk (43,44). Patients on long-term GC therapy should be examined for pain and decreased hip range of motion and magnetic resonance imaging (MRI) is warranted if symptoms are present (18,37). Osteonecrosis treatment includes bedrest, analgesics for pain and possible core decompression or in severe cases hip replacement (37). Alendronate had been suggested (45,46) as a treatment but a recent prospective randomized controlled trial showed no benefit (47).

SKIN

The skin can become atrophic and thin and exhibit purpura, which are reversible with discontinuation of therapy (48,49). However, red striae that may form are permanent. Wound healing can be significantly altered by GCs that impede leukocyte and macrophage activity and stunt collagen synthesis and wound maturation (49). Agents that can help reverse retarded wound healing because of the GC therapy include epidermal growth factor, transforming growth factor beta, platelet-derived growth factor, and tetrachlorodecaoxygen (48). Relative to striae, vitamin A 0.01% cream, pulsed dye laser and Thermage (non-ablative radiofrequency device) have shown some success of treatment (49). A low calorie diet may reduce the risk of forming striae.

INFECTIONS

The immunosuppressive properties of GC therapy increase risks of infection. A systematic review of 71 trials involving over 2,000 patients where GC treatment was random showed a significantly increased rate of infections (RR 1.6, 95% CI 1.3-1.9; $P < 0.001$) (50). If the dose was less than 10 mg of prednisone or a total amount less than 700 mg, the risk of infection was not increased (50). Steroid doses of greater than 15 mg/day in rheumatoid patients was found to significantly increase prosthetic joint infections (51). GC therapy also places patients at a higher risk for fungal and viral infections as well (48). It is also important to note that a heightened degree of suspicion for infections should be employed due to the decrease in the inflammation and febrile responses (52).

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia can occur within hours of the initiation (53), is dose-dependent and impacts postprandial glucose levels more so than fasting (54). A population-based study of 11,000 patients showed a significant dose dependent increase in hyperglycemia (55). High doses can increase insulin resistance in diabetes. Patients are treated just as you would diabetes without GC therapy (56,57). Hyperglycemia typically resolves when GC is discontinued but some patients will develop diabetes. Symptoms of polyuria, polydipsia, and

weight loss should be relayed to the patient. The Canadian Diabetes Association recommended that baseline glucose be evaluated and monitored for at least the first 48 hours after initiation of therapy (57). If GC therapy is initiated and significantly elevates blood glucose then referral to endocrinology for management should be considered.

EYE DISORDERS

Glaucoma and cataracts are both risks of GC therapy and it is dose dependent (a minimum of 1 year, and doses of >10 mg of oral prednisone) tends to cause the more severe posterior subcapsular cataracts requiring earlier surgical correction (58). These are also more common in local topical therapy than with oral treatment (59).

Glaucoma is the more serious sequelae involving the eye, although, this is more likely if there is a family or personal history of open angle glaucoma, diabetes, high angle myopia, or connective tissue disease more classically rheumatoid arthritis (60). If a patient is to receive long-term GC therapy referral to ophthalmology should be considered. All patients requiring >6 months GC therapy should have annual eye examinations and those at higher risk for glaucoma should be referred earlier.

GC therapy should also be avoided in patients with a history of central serous chorioretinopathy as this leads to separation of the retina from its photoreceptors (61). Symptoms include central blurring of vision and decreased acuity.

PSYCHIATRIC AND COGNITIVE DISTURBANCES

GC can cause memory loss, agitation, irritability, anxiety, fear, hypomania, insomnia, lethargy, mood changes, and even psychoses. These changes can occur as early as 1 week of therapy and is dose and duration dependent (62,63). The risk is increased with a family or personal history of depression or alcohol abuse (64). Initially, GC therapy tends to cause euphoria but longer therapy more likely results in depression (62,65,66).

Insomnia and unpleasant dreams can be minimized by morning dosing and night time sedative therapy (67). Self reported memory loss is dose dependent and can occur as early as 3 weeks (68). Partial loss of explicit memory is seen with >5 mg prednisone for at least 1 year (69).

Older patients are at higher risk for memory changes. Psychoses is seen at higher doses >20 mg prednisone for longer periods (70). Lithium has been shown to be helpful in GC patients for treatment or prophylaxis of affective disorders (71). Most patients recover fully from psychiatric disturbances with dose reduction or discontinuation of therapy.

CUSHINGOID CHANGES AND WEIGHT GAIN

Prolonged GC therapy can cause weight gain and Cushingoid changes (truncal obesity and increased adipose in dorsal cervical region). Weight gain was the most frequent self-reported adverse effect at 70% in long-term GC therapy in a survey of over 2,000 patients (>60 days of therapy) (72). These changes are dose and duration dependent. One study of 88 patients on >20 mg/day found rates of 61% at 3 months and 70% at 12 months (73). Weight gain was analyzed in 4 prospective clinical trials of rheumatoid patients showing an average weight gain of 4-8% while on 5-10 mg/day for 2 years (2).

GASTROINTESTINAL EVENTS

GC therapy has been linked to increases in gastritis, ulcer formation, dyspepsia, abdominal distension, and esophageal ulceration. A large meta-analysis of randomized controlled trials failed to show a significant relationship between GC and peptic ulcers (74,75). It appears that the risk of ulcers is related to combination therapy of GCs and nonsteroidal anti-inflammatory drugs (NSAIDs) (52). Two separate studies showed a 4-times greater rate of peptic ulcers in those using combination therapy versus those only taking GCs (76,77).

Pancreatitis has also been associated with GC use. A Swedish based study showed increased acute pancreatitis after GC use. This study showed an OR of 1.53 (95% CI 1.27-1.84) that had the greatest incidence between 4 and 14 days after starting therapy (78). However, other evidence implicates the underlying disease particularly SLE in lieu of the GC treatment as the cause (79).

CARDIOVASCULAR EVENTS

GCs associated with hypertension, hyperglycemia, and obesity all increase risks for cardiovascular (CV) disease. A large population-based study comparing 67,781 GC users versus 82,202 controls found CV events to be significantly higher in high dose users >7.5 mg/day of prednisone users (adjusted RR 2.56; 95% CI 2.18-2.99) (80). Another large retrospective study found GC to have a higher incidence of heart failure (adjusted OR 2.66, 95% CI 2.46-2.87) and ischemic heart disease (OR 1.20, 95% CI 1.11-1.29) but not ischemic stroke or transient ischemic attack (81).

Serious CV events that include arrhythmias (82,83) and sudden death have been associated with GC therapy. However, these are rare and most of these patients also had kidney and cardiac disease (84). Even though it is unclear if GC or the underlying conditions cause these CV events,

some experts recommend cardiac monitoring in patients with cardiac or kidney disease when getting IV pulse therapy (85).

Dyslipidemia data is conflicting. Clinical trials on SLE patients and GC doses >10 mg/day of prednisone show increased hyperlipidemia (86,87). Another study in rheumatoid arthritis patients failed to find an association when adjusted for other risk factors (88). The Third National Health and Nutrition Examination Survey of 15,004 patient found that GC may have a positive effect on lipid therapy in adults 60 years or older (89). Despite the lack of clear understanding of the risk, it is recommended that patients on high doses for longer periods should be monitored.

MYOPATHY

Corticosteroids have a catabolic effect on muscle that ultimately may result in muscle weakness. This usually takes between 3 weeks to 3 months to develop and in doses typically ≥10 mg/day (90). Patients will have proximal muscle weakness and atrophy but no myalgia or tenderness (85,91). The higher the dose the quicker this occurs. There is no test for myopathy so this is a diagnosis of exclusion. Dose reduction or discontinuation usually resolves the symptoms within 3 to 4 weeks (90). There is support for resistance and endurance exercise to ameliorate the atrophy and weakness (92).

Critical illness myopathy can occur in high dose IV therapy. Although typically reversible, it can lead to prolonged intensive care unit stays, severe necrotizing myopathy and increased mortality (85,91,93). Treatment includes discontinuing GCs and management of underlying conditions. Strategies for prevention of adverse events with GCs are listed in Table 3.

PEDIATRIC GC USE

All the previous adverse events apply to children. However unique to them is that GC therapy has been shown to cause delays in puberty and stunting of growth (94-98). In a study of 224 children with cystic fibrosis receiving alternate day prednisone versus placebo, the average age of treatment initiation was 9.5 years (range 6 -14) and termination was 12.9 years for high-dose and 13.8 for low-dose therapy. Patients were followed for an additional 6 to 7 years. Boys had a significant decrease in height whereas females did not. Due to the risk of growth suppression and the type of indications we use steroids in podiatric medicine, we do not use it in our practice for the pediatric population. We would recommend referral to rheumatology or endocrinology if there was a need to prescribe GCs for children.

CONCLUSION

GCs are powerful anti-inflammatories that do present a number of risks especially if taken for long periods of time AND at higher doses. Many of these side effects can be mitigated by using the minimum dose to treat. It is prudent to discuss the possible side effects and their symptoms and how to reduce risks through lifestyle changes. Patients should be advised to seek medical advice should they experience any adverse event.

It appears that by using GCs episodically at less than 2 weeks in 3 months or by using less than 10 mg/day most of the adverse events can be avoided. The potential for aseptic necrosis, although dose and duration dependent, can be increased with even 1 steroid dose pack. Although the overall rate of 0.132% with 1 dose pack is small, the risk is 1.5 times higher than in the control group. The use of steroids has to be weighed with these risks in mind and communicated to the patient.

Table 3. General strategies for avoiding adverse events.

- Treat comorbidities that may contribute to increase adverse events on GC's
- Prescribe the lowest dose over the shortest time to provide therapeutic effect
- Administer single am dose if possible
- Consider when possible alternate day or intermittent therapy
- Use GC sparring medications when possible
- Advise patients to:
  - Carry a steroid treatment card
  - Seek medical attention if they develop mood or behavioral changes
  - Avoid contact with infections especially measles, chickenpox or shingles (unless they are immune)
  - Do not abruptly stop GC therapy unless advised by a physician
  - Adopt lifestyle that minimizes weight gain and other adverse events
  - Eat healthy balanced diet with adequate calcium
  - Smoking cessation
  - Reduced alcohol consumption
  - Regular physical activity
- Monitor signs and symptoms of adverse events

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