A Comprehensive Review of the Adverse Effects of Systemic Corticosteroids

David M. Poetker, MD, MA[a,b,*], Douglas D. Reh, MD[c]

KEYWORDS

• Steroid • Prednisone • Corticosteroids • Glucocorticoids
• Adverse effects • Complications • Steroid physiology • Review

Corticosteroids are commonly prescribed by practitioners in many medical specialties for the treatment of chronic inflammatory conditions. The use of corticosteroids in the treatment of chronic rhinosinusitis is well described and based on their antiinflammatory effects.[1] The duration of corticosteroid therapy in these conditions is often less than 1 month, in contrast to the treatment of chronic respiratory diseases (ie, asthma, chronic obstructive pulmonary disease) or autoimmune disorders (ie, rheumatoid arthritis, systemic lupus erythematosus, Crohn disease, and ulcerative colitis), which can last for years.

Although systemic corticosteroids provide an effective therapy for chronic sinusitis, they also have associated adverse effects that have been well studied and described.[1–3] The objective of this article is to present a comprehensive review of the physiology of systemic corticosteroids and the known side effects associated with their use.

MORPHOLOGIC CHANGES

Redistribution of adipose tissue is a common effect associated with prolonged corticosteroid treatment (**Table 1**). These changes are known as cushingoid changes, and

[a] Division of Rhinology and Sinus Surgery, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA
[b] Department of Surgery, VA Medical Center, 5000 West National Avenue, Milwaukee, WI 53295, USA
[c] Division of Rhinology and Sinus Surgery, Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Medical Institutions, 601 North Caroline Street, Baltimore, MD 21287, USA
* Corresponding author. Division of Rhinology and Sinus Surgery, Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.
E-mail address: dpoetker@mcw.edu

Otolaryngol Clin N Am 43 (2010) 753–768
doi:10.1016/j.otc.2010.04.003 **oto.theclinics.com**
0030-6665/10/$ – see front matter. Published by Elsevier Inc.

Table 1
Summary of common complications following systemic corticosteroids

Complication	Signs/Symptoms	Comments
Morphologic changes	Cushingoid changes Truncal obesity Facial adipose tissue (moon facies) Dorsocervical adipose tissue (buffalo hump)	Variable reports about incidence and required dosage
Hyperglycemia	Increased blood sugar levels	Degree of increase in blood sugar level variable and not well characterized
Infection	Bacterial, fungal, and viral infections	Multiple effects on leukocytes Usually requires prolonged courses
Wound healing	Decrease monocytes/macrophages Delayed wound healing	Decrease phagocytosis and cytokine production Delay reepithelialization, decrease the fibroblast response, slow capillary proliferation, and inhibit collagen synthesis
Bone metabolism	Decrease bone density Avascular necrosis	Effect usually transient Can present months after use Reported after as few as 6 days Reported after as little as 290 mg prednisone (total dose)
Ophthalmic	Cataracts Glaucoma	Reported after as few as 2 months of use Usually requires months to years of use Up to 5% develop pressure increases within weeks
Skin changes	Dermal thinning, skin fragility, and ecchymosis Striae	Usually reversible with discontinuation Irreversible
Gastrointestinal	Peptic ulceration	No conclusive evidence to support associations Gastritis symptoms more common with steroid use

Adrenal suppression	Multiple systemic effects, blood pressure changes, water retention, lack of stress response	Individual variability in the dose that can lead to adrenal suppression Incidence of clinically evident adrenal insufficiency is believed to be much lower than the incidence based on objective measures
Myopathy	Type IIb muscle fiber atrophy	Usually involves the proximal limbs Usually resolves 1–4 months after steroid cessation
Cardiovascular	Increased blood pressure Myocardial infarction and cerebrovascular disease	Cause uncertain, usually transient Epidemiologic studies demonstrate increased risk Cause unclear
Psychiatric	Mild effects: agitation, anxiety, distractibility, fear, hypomania, indifference, insomnia, irritability, lethargy, mood lability, pressured speech, restlessness, and tearfulness	Incidence: 27.6% (range 13%–62%)
	Severe reactions: mania, depression (suicidal ideations), a mixed state, aggressiveness	Incidence: 5.7% (range 1.6%–50%) A past reaction is not predictive of a future reaction Past tolerance is not predictive of future tolerance Studies have not been able to correlate a history of psychiatric illness with a psychiatric reaction to prednisone Duration is variable Severe symptoms may take weeks to resolve More than 90% recover from these symptoms

include truncal obesity, facial adipose tissue referred to as moon facies, and dorsocervical adipose tissue referred to as buffalo hump.[4] The rate at which this occurs is variable. It has been reported to occur in 15% of patients in less than 3 months' time, with doses equivalent to 10 to 30 mg of prednisone per day.[4] A different study found that 13% of patients taking up to 12 mg of prednisone daily for more than 60 days developed moon facies, with up to 66% of the patients demonstrating this complication from corticosteroid use over 5 years.[5] A meta-analysis of randomized controlled trials found that these changes occur more frequently in patients receiving steroids than in patients receiving placebos.[6] Higher doses and longer duration of corticosteroid use seem to increase the frequency of adipose tissue redistribution. Patients taking daily prednisone demonstrated adipose redistribution or corticosteroid-induced lipodystrophy at incidences of 61%, 65%, and 69% at 3, 6, and 12 months, respectively, with mean doses of 32 mg, 19 mg, and 11 mg at the respective time points.[7] This study further demonstrated that the risk was higher in women, patients less than 50 years of age, and patients with either a high initial body mass index or a high calorie intake.

HYPERGLYCEMIA

Corticosteroids increase blood sugar levels by increasing hepatic gluconeogenesis and by decreasing glucose uptake in peripheral tissues.[8] Corticosteroids stimulate proteolysis, promote the release of gluconeogenesis-stimulating enzymes, and inhibit adipose and muscle tissue glucose uptake.[8] Furthermore, acute exposure to corticosteroids causes insulin resistance by decreasing the ability of adipocytes and hepatocytes to bind insulin. This effect can occur within 12 hours of beginning therapy, although it has been found to decrease with prolonged corticosteroid use.[8] Synthetic corticosteroids such as prednisone and dexamethasone are 4 and 30 times more potent, respectively, than natural corticosteroids such as hydrocortisone at decreasing carbohydrate tolerance.[8]

Correlations have also been made to steroid dose and the development of diabetes, with daily and cumulative dose likely independent risk factors.[4] Several studies have demonstrated a statistical correlation between hyperglycemia and exogenous corticosteroid use.[4,6,8,9] On cessation of corticosteroids, the inhibition of glucose uptake and metabolism in peripheral tissues usually returns to normal.[8] Despite their common use, the effect on blood glucose levels and the degree of hyperglycemia caused by steroids have not been clearly elucidated.

INFECTION

The mechanism by which corticosteroids decrease inflammation may also lead to immunosuppressive effects. Steroids decrease the peripheral concentration and function of leukocytes. Whereas circulating neutrophils increase as a result of enhanced release from bone marrow and reduced migration from blood vessels, the number of other leukocytes such as lymphocytes, monocytes, basophils, and eosinophils decrease. This decrease in peripheral leukocytes is a result of a migration from the vascular bed to lymphoid tissue.[10] Corticosteroids can further affect neutrophil function by reducing their adherence to vascular endothelium as well as their bactericidal activity.[11] Corticosteroids further inhibit the function of macrophages and other antigen-presenting cells by limiting chemotaxis, phagocytosis, and the release of cytokines such as tumor necrosis factor α and interleukin-1.[10,11] Corticosteroids have also been shown to decrease the expression of inflammatory mediators such as prostaglandin, leukotriene, and platelet-activating factor, and at higher doses

have been shown to inhibit B-cell production of immunoglobulins.[10,11] The administration of corticosteroids on an alternate days has been shown to reduce their negative impact on leukocyte function.[11]

A meta-analysis by Stuck and colleagues[12] reviewed 71 clinical studies to assess for the relative risk of corticosteroids on the rate of infections. They found that the overall rate of infections was 8.0% in the control group and 12.7% in patients receiving corticosteroids, a statistically significant increase. Their review found that patients who received a daily dose of less than 10 mg per day or a cumulative dose of less than 700 mg of prednisone did not have an increased rate of infectious complications.[12]

A meta-analysis of more than 8700 patients by Conn and Poynard[6] found that bacterial sepsis occurred 1.5 times more frequently in patients using corticosteroids than in those using placebo ($P<.01$). The mean daily dose was the equivalent of 35 mg of prednisone and the mean total dose was 2200 mg of prednisone for these patients.[6] Although the disease processes for which the patients are being treated may themselves be independent risk factors for increased infection, few studies in the aforementioned meta-analyses included patients with autoimmune diseases, which are known risk factors for increased infections.[6,12]

Several studies have demonstrated that patients treated with glucocorticoids are at increased risk for developing invasive fungal infections, pneumocystosis, and viral infections, especially in patients who have undergone bone marrow transplantation.[4,13–17] O'Donnell and colleagues[13] retrospectively reviewed 331 allogeneic bone marrow recipients and found that the major risk factor for candidemia or aspergillosis was prednisone treatment (0.5–1 mg/kg/d). None of the 36 cases of systemic fungal infections were in the paranasal sinuses. Several studies from the Fred Hutchinson Cancer Research Center and University of Washington demonstrate an increased risk of invasive mold infections (including *Aspergillus* and Zygomycetes) as well as an increased risk of death from these infections in bone marrow transplant patients receiving high-dose corticosteroids ($\geq$2 mg/kg/d prednisone or methylprednisolone).[14,16,17]

WOUND HEALING

Wound healing occurs in an orderly fashion. The initial response to a surgical injury is an inflammatory reaction in which the wound is invaded by polymorphonuclear leukocytes and lymphocytes. These cells are then replaced by macrophages from circulating blood monocytes. The presence of the macrophages is essential for normal wound healing. Within 48 hours, reepithelialization and angiogenesis occur as part of the proliferation phase, which includes extensive capillary budding and proliferation of fibroblasts in the wound site. Collagen deposition begins within 4 or 5 days, and is responsible for the initial wound strength. Collagen deposition is followed by the formation of covalent bonds and scar remodeling, which leads to additional wound strength and maturation.[18]

Corticosteroids inhibit the natural wound-healing process in several ways. First, they decrease the circulating monocytes, thus decreasing the influx of macrophages.[18,19] Studies suggest that the reduced number of macrophages may decrease phagocytosis as well as growth factor/cytokine production.[20,21] In addition, corticosteroids can delay reepithelialization, decrease the fibroblast response, slow capillary proliferation, and inhibit collagen synthesis and wound maturation,[18,20,22] ultimately leading to delayed wound healing and decreased tensile strength.[22]

Several topical and systemic agents such as epidermal growth factor, transforming growth factor β, platelet-derived growth factor, and tetrachlorodecaoxygen have been shown to counteract the effect of corticosteroids on wound healing.[18] Systemic agents such as vitamin A and insulinlike growth factor 1 also may counter the impact of corticosteroids on wound healing.[21]

BONE METABOLISM

The role of steroids in bone loss is well described and may occur through several different mechanisms. First, they cause a negative calcium balance via an anti–vitamin D effect by reducing intestinal calcium absorption and increasing urinary calcium excretion. This negative calcium balance stimulates parathyroid hormone production, which increases osteoclast activity, accelerates bone absorption, and releases calcium into the circulation at the expense of bone mass. In addition, steroids inhibit osteoblast activity, negatively affecting trabecular bone formation. This effect places bones, such as vertebral bodies, femoral necks, and distal radii, at increased risk for fracture.[23,24]

Corticosteroids also suppress the production of adrenal androgens, decreasing their beneficial effect on bone formation. Prednisone doses higher than 20 mg per day decrease the production of gonadotropin-releasing hormone, which decreases the production of luteinizing hormone, leading to a secondary hypogonadism state. This secondary hypogonadism decreases testosterone production, further decreasing bone formation and increasing bone resorption.[24]

Corticosteroids have been found to cause apoptosis of osteoblasts and osteocytes. This effect has been shown to occur within 1 month of use; however, it slows after 6 to 12 months.[25] A reduction in bone formation based on markers of bone metabolism has been demonstrated with as little as 5 mg of prednisone daily for as short as 2 weeks.[25,26] van Staa and colleagues[26] found a dose-related reduction in osteocalcin levels, a marker of bone formation, within the first 24 hours of prednisone therapy. This effect was rapidly reversible with cessation of prednisone therapy.

Paglia and colleagues[27] studied bone resorption and formation in 14 elderly men who were placed on courses of prednisone for less than 30 days at a mean cumulative dose of 338 mg of prednisone. The investigators found statistical differences in the steroid group, with significant increases in markers of bone turnover and decreases in markers of bone formation. In addition, osteocalcin levels were inversely correlated with the cumulative dose of prednisone.[27] A second study measured the dose-related changes in serum osteocalcin in patients with asthma on a 12-day course of oral prednisolone with doses increasing every 4 days.[28] They found that after 4 days of 5 mg daily, there were no significant differences in osteocalcin levels; however, a significant decrease was noted after 10 mg, and the levels continued to decrease after daily doses of 20 mg.[28]

The clinical significance of these changes in markers of bone metabolism as they relate to changes in bone mineral density has been debated. A study performed by Laan and colleagues[29] compared bone mineral densities in patients treated with or without corticosteroids for their rheumatoid arthritis. The investigators found that postmenopausal women taking a mean daily dose of 6.8 mg of prednisone (mean cumulative dose was 22.5 g) for a mean duration of 7.9 years (range 1.1–31.9) had a statistically significant decrease in trabecular bone mineral density, cortical bone mineral density, and a statistically significant increase in vertebral deformities compared with patients not using prednisone. Male patients taking a mean daily dose of 7.1 mg of prednisone for a mean duration of 4.2 years (range 0.9–9.2) had

no statistically significant difference in bone mineral density or vertebral deformities compared with patients not using prednisone.[29] Although these data conflict with earlier studies, the investigators used quantitative computed tomography, which is more accurate than traditional bone density studies in assessing bone mineral densities. Limitations of this study include insufficient premenopausal women to include for statistical analysis, a relatively small sample size, and the fact that patients receiving prednisone had clinically more severe rheumatoid arthritis, which itself is a risk factor for reduced bone mineral density.

Data are conflicting as to whether daily dose or cumulative dose has a more significant clinical effect on bone density. A meta-analysis by van Staa and colleagues[26] demonstrated a stronger correlation between cumulative steroid dose on bone mineral density than daily dose. Fracture risks have also been shown to increase based on dose, duration, age, gender, and body weight.[4] Several studies have demonstrated that supplemental calcium and vitamin D, as well as bisphosphonates can help reduce the corticosteroid-induced loss of bone mineral density.[4]

Corticosteroid use has also been associated with avascular necrosis or osteonecrosis. This complication has been correlated with cumulative dose, and has been seen primarily in the head of the femur, although other weight-bearing and non–weight-bearing bones can be affected.[23] The exact cause is not fully understood, but is thought to include embolic events in the blood supply, a hyperviscous state of the blood, cellular cytotoxic factors, hypertrophy of marrow fat cells, which increases the pressure in the femoral head, resulting in decreased blood flow, or generation of bone edema, all leading to impaired perfusion of the bone.[23,30,31]

A retrospective review of patients treated for osteonecrosis of the femoral head in an orthopedic clinic identified 15 patients who had been treated with a single course of glucocorticoids over a 3-year period, before presentation.[32] All patients were male; 13 had received prednisone, 2 dexamethasone. The mean age was 32.2 years (range 20–41 years), the mean cumulative dose was 850 mg of prednisone (range 290–3300 mg), and the mean duration of therapy was 20.5 days (range 6–39 days). The patient who presented after the lowest cumulative dose of prednisone, 290 mg in 7 days, was one of the latest presenters. He presented with pain 23 months after corticosteroid treatment for poison ivy. The mean time from treatment to symptoms in the study was 16.6 months (range 6–33 months).[32] Another retrospective series of 1352 patients treated with corticosteroids for neurosurgical issues identified 4 cases of avascular necrosis, a risk of 0.03%. The mean age was 26 years (range 21–31 years), the mean cumulative dose was equivalent to 673 mg of prednisone (range 389–990 mg of prednisone equivalents), and the mean duration was 20 days (15–27 days).[33] The time for onset of symptoms in this group ranged from 4 to 27 months, with a mean of 14.5 months.

OPHTHALMIC

Corticosteroids can have extensive ophthalmic effects, depending on the route of administration. Systemic administration of corticosteroids can lead to cataract formation, increased intraocular pressure, myopia, exophthalmos, papilledema, central serous chorioretinopathy, and subconjunctival hemorrhages.[34] The most commonly encountered ophthalmologic side effects include cataract formation and increased intraocular pressure or glaucoma. The correlation between corticosteroids and posterior subcapsular cataracts was first described in the 1960s, with the incidence dependent on dose and duration of corticosteroid use. Although studies have shown that doses as low as 5 mg of oral prednisone taken for as little as 2 months can lead to

cataracts, most report doses of 10 mg or more daily for at least 1 year before the onset of cataract formation.[34] Many causes of steroid-induced cataract formation have been proposed. One theory suggests that steroid molecules bond covalently with the lysine residues of the lens, leading to opacities. Another proposed mechanism states that corticosteroids inhibit the sodium-potassium pump in the lens, leading to an accumulation of water and coagulation of lens proteins.[34]

Increased intraocular pressure can lead to visual field loss, optic disk cupping, and optic nerve atrophy. The correlation between increased intraocular pressure and glaucoma was first identified in the early 1950s.[34] Corticosteroids cause significant increases in intraocular pressure in approximately 5% of patients within the first few weeks of therapy.[24] Eventually, between 18% and 36% of the population will develop at least a moderate (5 mm Hg or greater) increase in pressure with prolonged steroid treatment.[24] Factors associated with a greater risk of increased intraocular pressure induced by corticosteroids include open-angle glaucoma, diabetes mellitus, high myopia, rheumatoid arthritis, hypertension, migraine headaches, and first-degree relatives with open-angle glaucoma.[24,34] The route of administration seems to play an important role; topical ophthalmic and systemic administration have a high correlation with the incidence of glaucoma. The exact mechanism by which corticosteroids cause glaucoma is unknown. One theory suggests that corticosteroids may have a negative effect on the trabecular meshwork by causing the buildup of proteins such as glycosaminoglycans, fibronectin, elastin, laminin, and collagens or by preventing the appropriate expression of prostaglandins, collagenase, plasminogen activator, and stromelysin, enzymes that help break down outflow obstructions.[24,34] When the trabecular meshwork does not allow for proper drainage, fluid is retained and pressures increase.

SKIN CHANGES

Cutaneous complications caused by corticosteroids include Cushing syndrome, skin atrophy, striae, ecchymoses, and changes in mechanical properties of the skin. Less commonly, pustular acne, tinea incognito, and Stevens-Johnson syndrome may occur.[24] Corticosteroids cause a reduction in mitotic activity of the keratinocytes in the germinal layer and flattening of the rete ridges. They may also cause a loss of ground substance and reduction of fibroblast size. These changes ultimately cause thinning of the dermis and increase the fragility of the skin. In some cases, a steroid effect on microvascular endothelial cell development causes telangiectasia formation, whereas the loss of ground substance decreases the structural support for vessels and increases their dilation, leading to ecchymosis.[24] Atrophy and ecchymoses are often reversible on the discontinuation of corticosteroids, but striae are not. Striae are visible linear scars that occur as a result of inflammation and edema of the dermis. Collagen and elastin are then deposited along these lines of mechanical stress, causing scar tissue formation.[24]

The frequency with which these complications occur is not entirely understood; however, they seem to be more common with systemic corticosteroids than topical or inhaled corticosteroids. One study demonstrated cutaneous changes in 37 of 80 (46%) patients on a mean dose of 31 mg of prednisone over 3 months. These changes included hirsutism, spontaneous bruising, and altered wound healing. Of the patients with hirsutism, all were female, and the risk tended to increase with age.[35] A second study demonstrated almost a 5-fold increase in ecchymoses with corticosteroid use; another study found a 4-fold increase in the frequency of Cushing syndrome, acne, and hirsutism.[5]

GASTROINTESTINAL

Despite the commonly held perception that steroid use increases the risk of peptic ulcer disease, several large meta-analyses of randomized, placebo-controlled trials have failed to show this association.[5] Specifically, Conn and Blitzer[36] performed a meta-analysis of 26 placebo-controlled, randomized clinical trials and found no correlation between corticosteroid use and peptic ulcer disease. This study was followed by a meta-analysis of 71 similar placebo-controlled, randomized clinical trials by Messer and colleagues.[37] This study demonstrated a 2-fold increase in peptic ulcer disease with corticosteroid use. Messer's data were reviewed by Conn and Poynard who could not find a statistically significant association. They performed a follow-up meta-analysis of 93 randomized, double-blind, placebo-controlled trials and found no statistically significant association between ulcer development and prednisone use.[6] These studies did find that patients using prednisone complained of peptic ulcer–type symptoms more frequently than the control patients. The investigators suggest that this could be due to superficial ulcers that were not deep enough to be detected by barium studies in the pre-endoscopic era.[6] The lack of association between corticosteroids and peptic ulcer disease was confirmed by Piper and colleagues.[38]

In addition to gastric issues, pancreatitis has been reported with the use of corticosteroids.[4] The exact incidence and the mechanism by which the corticosteroids cause pancreatitis is unknown.

ADRENAL SUPPRESSION

In the normal, nonstressed adult, the adrenal gland secretes 10 to 20 mg of cortisol per day, which translates to approximately 5 to 7 mg of prednisone per day.[10,39] Exogenous steroids increase the circulating corticosteroid levels, which can lead to a negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis at the levels of the hypothalamus and the pituitary gland. This effect can lead to a decrease in production of corticotropin-releasing hormone from the hypothalamus and corticotropin or adrenocorticotropic hormone from the pituitary gland.[40] Decreased production of adrenocorticotropic hormone then leads to decreased cortisol secretion from the adrenal cortex.

There seems to be inconsistency in the dose of exogenous corticosteroids that can lead to adrenal suppression. This inconsistency is believed to be due to individual variability, as well as the specific synthetic corticosteroid administered, with some having a more dramatic effect than others.[4,41] Post mortem studies have shown atrophy of adrenal glands following as few as 5 days of corticosteroid therapy.[4] A retrospective review of rheumatologic patients identified no definitive cases of adrenal suppression with prednisone doses less than 5 mg per day, even if that dose is taken for many months.[42] The study previously referenced by Wilson's group demonstrated no significant decreases in plasma cortisol levels following a 4-day course of 5 mg of prednisolone daily.[28] When the doses were increased to 10 mg and then to 20 mg per day, each for 4 days, there was a significant decrease in plasma cortisol levels.[28]

Other studies have demonstrated that short courses for less than 30 days, with doses ranging from 15 to 50 mg of prednisone per day, can result in significant adrenal suppression in patients.[4] This suppression can then last for many weeks after the course is completed. Longer-term, lower-dose synthetic corticosteroids can also lead to adrenal insufficiency, requiring months for adrenal recovery.[4] The incidence of clinically evident adrenal insufficiency is unknown but it is believed to be much lower than the incidence based on objective measures.[4]

MYOPATHY

Muscle weakness associated with corticosteroid use is believed to be caused by type IIb muscle fiber atrophy.[4,5,43] Corticosteroids interfere with skeletal muscle oxidative phosphorylation, protein synthesis, muscle membrane excitability, and carbohydrate metabolism.[4,43] The onset is usually asymptomatic with the muscles of the proximal limbs affected first.[44] Rarely are the distal limb muscles, sphincters, or facial muscles affected, and smooth muscle does not seem to be involved at all. Patients often notice difficulty with tasks such as climbing stairs. This effect gradually resolves over 1 to 4 months after cessation of the corticosteroids and affected muscles regain their strength.[44] This effect has been shown to be dose dependent, with the corticosteroid effect lasting from days to months after the cessation of therapy.[4]

One study demonstrated a 64% incidence of muscle weakness on formal muscle testing in patients with asthma taking more than 40 mg of prednisone daily and a 12% incidence in those taking less than 40 mg of prednisone daily.[44] Although myopathy was worse in patients using more than 40 mg daily, doses as low as 10 mg daily, dosing every other day, and recurrent bursts of prednisone all caused evidence of muscle weakness in some patients.[44] These results are consistent with a case-control study that demonstrated a 6.7-fold increase in reported frequency of muscle weakness in patients with lung disease taking corticosteroids for longer than 6 months.[45] The latter study demonstrated increased risk of muscle weakness with increased daily and cumulative doses of prednisolone.[45] Other studies have contradicted these results. Picado and colleagues[46] demonstrated no significant difference in respiratory or skeletal muscle force, endurance, or histologic appearance in patients with asthma taking an average daily dose of approximately 12 mg of prednisone (mean duration approximately 8 years) compared with those not using oral prednisone.

CARDIOVASCULAR

Corticosteroids have been associated with increases in blood pressure, although the mechanisms have not been clearly elucidated. One debated theory is that mineralocorticoids increase plasma volume by binding to mineralocorticoid receptors in the renal distal tubular epithelial cells, resulting in increased sodium reabsorption and water retention with subsequent extracellular volume expansion.[4,5,47] The incidence of secondary hypertension due to corticosteroids has not been adequately described. One study did look at individuals taking mean daily doses of prednisone between 6.7 mg and 8.4 mg, and found no association with the development of hypertension.[5] The Conn and Poynard meta-analysis demonstrated a statistically significant increase in hypertension in those patients treated with corticosteroids.[6]

Two large observational studies from the United Kingdom analyzed the correlation between systemic corticosteroids and cardiovascular disease.[48,49] Both studies demonstrated significant increases in the risk of myocardial infarction and cardiovascular disease with the use of systemic corticosteroids. This risk increased in both studies based on average daily dose; however, only the Wei study demonstrated an increased risk with a higher cumulative dose. Only 1 of the 2 studies demonstrated an increased risk of cerebrovascular disease with the use of corticosteroids; the second reported a slight decrease in the risk of cerebrovascular disease.[48,49] This risk was found to be associated with cumulative dose, and seemed to be higher in patients with increased baseline risk such as cardiac or pulmonary disease.

PSYCHIATRIC

Corticosteroids cause cognitive as well as psychiatric disturbances. Cognitive deficits, such as memory disturbances, may emerge as early as 4 days after starting steroids, and appear to be dose dependent and reversible on termination of the medication.[50] The most common psychiatric manifestations include agitation, anxiety, distractibility, fear, hypomania, indifference, insomnia, irritability, lethargy, mood lability, pressured speech, restlessness, and tearfulness. Most psychiatric side effects occur within the first week of therapy and the time of onset has not been correlated with dose.[51] Although these effects can cause significant detriment to an individual's daily quality of life, they are not considered severe reactions. Severe reactions include mania, depression, or a mixed state.[50] Most individuals developing psychiatric manifestations on short courses report euphoria or hypomania, whereas those on long-term therapy tend to develop depressive symptoms.[50]

There is a dramatic variability in the incidence of steroid-induced psychiatric side effects reported in the literature, reflective of the unpredictability of these reactions, the wide range of steroid doses, and inconsistencies in effect definitions. A meta-analysis reported an incidence of 27.6% (range 13%–62%) of individuals who experienced mild to moderate psychiatric complications from corticosteroid use, whereas only 5.7% (range 1.6%–50%) reported severe complications.[52]

Corticosteroid dose was found to be the most significant risk factor associated with psychiatric reactions, with 1 series of 676 patients reporting a 3.1% incidence. Of the patients with acute psychiatric reactions, 62% demonstrated inappropriate euphoria, 9.5% were severely depressed, and 28.6% were maniacal.[53] When psychiatric symptoms were analyzed based on prednisone dose, there was a 1.3% incidence in those patients receiving a daily prednisone dose less than or equal to 40 mg, a 4.6% incidence in those receiving 41 to 80 mg of prednisone, and an 18.4% incidence in those receiving more than 80 mg.[53] The investigators found that reduction of the dose resulted in resolution of symptoms in all cases. A past reaction is not predictive of a future reaction, nor is past tolerance of prednisone predictive of future tolerance.[50] Additional studies have not been able to correlate a history of psychiatric illness with a psychiatric reaction to prednisone.[51]

The association between corticosteroids and psychiatric side effects was supported by the meta-analysis of Conn and Poynard. They reported that with a mean daily dose of 35 mg of prednisone, psychiatric side effects occurred 2 times more often than in those receiving placebo ($P<.02$).[6] A smaller prospective study found similar results, with more than half of the 80 patients demonstrating neuropsychiatric disorders during their 3-month course of prednisone (>30 mg per day).[35] Most of these reactions occurred early in the course of therapy, and most involved irritability and anxiety. However, 6 patients had severe episodes, 5 of whom required hospitalization. Of the 6, 3 had severe manic episodes, 2 had severe depression with suicidal thoughts, and 1 had aggressiveness.[35] Of these 6, only 1 patient had a history of minor depression.

Duration of the psychiatric disturbance is variable with delirium resolving within days, whereas severe symptoms such as depression or mania may take up to 6 weeks to resolve.[50] More than 90% of individuals with psychiatric reactions to corticosteroids recover from these symptoms.[51] Patient education about potential psychiatric side effects is crucial for early reporting and management.

TOPICAL PREPARATIONS

Topical use of corticosteroids is a common practice among otolaryngologists. These topical preparations can include more potent corticosteroids such as betamethasone

and dexamethasone, each with several times the glucocorticoid potency of prednisone, as well as higher concentrations of commonly used topical steroids such as budesonide.[54] Regardless of the specific preparation, the goal is to deliver a high dose of corticosteroid to the tissues without the systemic side effects.

The systemic effects of these medications are determined by their bioavailability after topical administration as well as the degree to which they are metabolized by the first pass effect in the liver. It is commonly believed that approximately 30% of the topically applied nasal steroid sprays stay in the nasal cavity and can thus be absorbed.[55] The exact amount that becomes systemically absorbed is difficult to ascertain. The remaining 70% is distributed to the oropharynx and swallowed, either directly or through the mucociliary clearance of the sinonasal epithelium. The ingested drug gets absorbed by the gastric mucosa and passes to the liver where the amount metabolized by the liver varies by agent. Traditional topical medications such as mometasone furoate and fluticasone propionate have exceptionally small bioavailabilities, each less than 1%, whereas beclomethasone dipropionate has a much higher bioavailability of 44%.[56] Budesonide, when used intranasally, has approximately 34% bioavailability.[57] Dexamethasone and betamethasone are believed to have even higher bioavailabilities.

The effect of topical intranasal sprays on the HPA axis has been studied extensively.[58–61] There have been more than a dozen studies measuring adrenal suppression in adults and children as young as 2 years of age that have demonstrated no effect on the HPA axis from the aforementioned intranasal corticosteroid sprays.[59]

There are at least half a dozen case reports in the literature discussing adrenal suppression and/or Cushing syndrome with the use of more potent topical preparations such as betamethasone or dexamethasone drops.[62–66] It was hypothesized that dexamethasone may have a high rate of direct absorption through the nasal and respiratory mucosa in addition to the uptake in the gastrointestinal tract.[66] Many of these cases were believed to be caused by medication overdosing, which can occur as a result of inconsistent dosing and delivery from the use of drops.[67]

Two recent studies have investigated the effect of budesonide nasal irrigations on the HPA axis. Sachanandani and colleagues[68] assessed the adrenal function of 9 patients before and after 30 days of topical budesonide. Patients were asked to mix 0.25 mg of budesonide with 5 mL of saline, then administer 5 mL of the mixture into their nasal cavity. Using the cosyntropin stimulation test, the investigators were unable to identify any evidence of adrenal suppression. Similarly, Welch and colleagues[69] demonstrated no evidence of adrenal suppression using serum cortisol and 24-hour urinary cortisol in 10 patients irrigating their sinuses with 0.5 mg of budesonide mixed into 240 mL of saline solution twice daily.

There have been at least 2 reports of significant growth retardation that correlated with the use of the betamethasone drops intranasally.[64] Both patients demonstrated a return to normal growth velocity once the betamethasone use was stopped. However, the patients were not observed long enough to determine their adult stature.[64]

SUMMARY

This article presents a comprehensive review of the side effects of exogenous corticosteroids and their relative frequencies. Otolaryngologists commonly prescribe corticosteroids to treat various conditions and diseases. For this reason, it is essential that the specific effects of these drugs, including their relative frequencies, severities, and associated doses, are better understood. It is also imperative that the informed

consent process includes the more significant and more common reactions described here. Unfortunately, there exists a paucity of data on the adverse effects associated with shorter courses and smaller doses of corticosteroids. Further prospective studies analyzing these effects are necessary.

REFERENCES

1. Nadel DM. The use of systemic steroids in otolaryngology. Ear Nose Throat J 1996;75:502–5 509–10, 511-2 passim.
2. Wright ED, Agrawal S. Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel perioperative sinus endoscopy (POSE) scoring system. Laryngoscope 2007;117(Suppl 115):1–28.
3. Cope D, Bova R. Steroids in otolaryngology. Laryngoscope 2008;118:1556–60.
4. Fardet L, Kassar A, Cabane J, et al. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. Drug Saf 2007;30:861–81.
5. McEvoy CE, Niewoehner DE. Adverse effects of corticosteroid therapy for COPD. Chest 1997;111:732–43.
6. Conn HO, Poynard T. Corticosteroids and peptic ulcer: metaanalysis of adverse events during steroid therapy. J Intern Med 1994;236:619–32.
7. Fardet L, Cabane J, Lebbé C, et al. Incidence and risk factors for corticosteroid-induced lipodystrophy: a prospective study. J Am Acad Dermatol 2007;57: 604–9.
8. Hirsch IB, Paauw DS. Diabetes management in special situations. Endocrinol Metab Clin North Am 1997;26:631–45.
9. Greenstone MA, Shaw AB. Alternate day corticosteroid causes alternate day hyperglycemia. Postgrad Med J 1987;63:761–4.
10. Chrousos GP. Adrenocorticosteroids & adrenocortical antagonists. In: Katzung BG, editor. Basic & clinical pharmacology. 10th edition. New York (NY): McGraw-Hill; 2007. p. 635–52.
11. Segal BH, Sneller MC. Infectious complications of immunosuppressive therapy in patients with rheumatic diseases. Rheum Dis Clin North Am 1997;23:219–37.
12. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989;11:954–63.
13. O'Donell MR, Schmidt GM, Teftmeier BR, et al. Prediction of systemic fungal infection in allogeneic marrow recipients: impact of amphotericin prophylaxis in high-risk patients. J Clin Oncol 1994;12:827–34.
14. Fukada T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 2003;102:827–33.
15. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003;362:1828–38.
16. Upton A, Kirby KA, Carpenter P, et al. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis 2007;44:531–40.
17. Marr KA, Carter RA, Boeckh M, et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002;100: 4358–66.
18. Atkinson JB, Kosi M, Srikanth MS, et al. Growth hormone reverses impaired wound healing in protein-malnourished rats treated with corticosteroids. J Pediatr Surg 1992;27:1026–8.

19. Nguyen H, Lim J, Dresner ML, et al. Effect of local corticosteroids on early inflammatory function in surgical wound of rats. J Foot Surg 1998;37:313–8.
20. Goforth P, Gudas CJ. Effects of steroids on wound healing: a review of the literature. J Foot Surg 1980;19:22–8.
21. Suh DY, Hunt TK, Spencer EM. Insulin-like growth factor-I reverses the impairment of wound healing induced by corticosteroids in rats. Endocrinology 1992; 131:2399–403.
22. Lenco W, McKnight M, MacDonald AS. Effects of cortisone acetate, methylprednisolone and medroxyprogesterone on wound contracture and epithelialization in rabbits. Ann Surg 1975;181:67–73.
23. Keenan GF. Management of complications of glucocorticoid therapy. Clin Chest Med 1997;18:507–20.
24. Allen DB, Bielory L, Derendorf H, et al. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol 2003;112:S1–40.
25. Ton FN, Gunawardene SC, Lee H, et al. Effects of low-dose prednisone on bone metabolism. J Bone Miner Res 2005;20:464–70.
26. van Staa TP, Leufkens HGM, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002;13:777–87.
27. Paglia F, Dionisis S, De Geronimo S, et al. Biomarkers of bone turnover after a short period of steroid therapy in elderly men. Clin Chem 2001;47:1314–6.
28. Wilson AM, McFarlane LC, Lipworth BJ. Systemic bioactivity profiles of oral prednisolone and nebulized budesonide in adult asthmatics. Chest 1998; 114:1022–7.
29. Laan RFJM, Van Riel PLCM, Van Erning LJTO, et al. Vertebral osteoporosis in rheumatoid arthritis patients: effects of low dose prednisone therapy. Br J Rheumatol 1992;31:91–6.
30. Cui Q, Wang G-J, Balian G. Steroid-induced adipogenesis in a pluripotential cell line from bone marrow. J Bone Joint Surg Am 1997;79:1054–63.
31. Mirzai R, Chang C, Greenspan A, et al. The pathogenesis of osteonecrosis and the relationship to corticosteroids. J Asthma 1999;36:77–95.
32. McKee MD, Waddell JP, Kudo PA, et al. Osteonecrosis of the femoral head in men following short-course corticosteroid therapy: a report of 15 cases. CMAJ 2001; 164:205–6.
33. Wong GK, Poon WS, Chiu KH. Steroid-induced avascular necrosis of the hip in neurosurgical patients: epidemiological study. ANZ J Surg 2005;75:409–10.
34. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophthalmol 2000;11:478–83.
35. Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. Br J Dermatol 2007;157: 142–8.
36. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976;294:434–79.
37. Messer J, Reitman D, Sacks H, et al. Association of adrenocorticosteroid therapy and peptic ulcer disease. N Engl J Med 1983;309:21–4.
38. Piper J, Ray W, Daugherty J, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;114:735–40.
39. Asare K. Diagnosis and treatment of adrenal insufficiency in the critically ill patient. Pharmacotherapy 2007;27:1512–38.
40. Ganong WF. The adrenal medulla & adrenal cortex. In: Ganong WF, editor. Review of medical physiology. 22nd edition. New York (NY): McGraw-Hill; 2007. p. 356–81.

41. Downie WW, Dixon JS, Lowe JR, et al. Adrenocortical suppression by synthetic corticosteroid drugs: a comparative study of prednisolone and betamethasone. Br J Clin Pharmacol 1978;6:397–9.
42. LaRochelle GE, LaRochelle AG, Ratner RE, et al. Recovery of the hypothalamic-pituitary-adrenal axis in patients with rheumatic diseases receiving low-dose prednisone. Am J Med 1993;95:258–64.
43. Polsonetti BW, Joy SD, Laos LF. Steroid-induced myopathy in the ICU. Ann Pharmacother 2002;36:1741–4.
44. Bowyer SL, LaMothe MP, Hollister JR. Steroid myopathy: incidence and detection in a population with asthma. J Allergy Clin Immunol 1985;76:234–42.
45. Walsh LJ, Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. Thorax 2001;56:279–84.
46. Picado C, Fiz JA, Montserrat JM, et al. Respiratory and skeletal muscle function in steroid-dependent bronchia asthma. Am Rev Respir Dis 1990;141:14–20.
47. Nussberger J. Investigating mineralocorticoid hypertension. J Hypertens 2003; 21:S25–30.
48. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141: 764–70.
49. Souverein PC, Berard A, Van Staa TP, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. Heart 2004;90:859–65.
50. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc 2006;81:1361–7.
51. Kershner P, Wang-Cheng R. Psychiatric side effects of steroid therapy. Psychosomatics 1989;30:135–9.
52. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. J Affect Disord 1983;5:319–32.
53. The Boston Collaborative Drug Surveillance Program Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther 1972;13:694–8.
54. Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Brunron LL, Lazo JS, Parker KL, editors. Goodman & Gilman's the Pharmacological basis of therapeutics, 11th edition.
55. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf 2000;23:11–33.
56. Daley-Yates PT, Kunka RL, Yin Y, et al. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. Eur J Clin Pharmacol 2004;60: 265–8.
57. Demoly P. Safety of intranasal corticosteroids in acute rhinosinusitis. Am J Otolaryngol 2008;29:403–13.
58. Bachert C, Lukat KF, Lange B. Effect of intranasal fluticasone propionate and triamcinolone acetonide on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity in healthy volunteers. Clin Exp Allergy 2004;34: 85–90.
59. Galant SP, Melamed IR, Nayak AS, et al. Lack of effect of fluticasone propionate aqueous nasal spray on the hypothalamic-pituitary-adrenal axis in 2- and 3-year-old patients. Pediatrics 2003;112:96–100.
60. Wilson AM, Sims EJ, McFarlane LC, et al. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol 1998;102:598–604.

61. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. Drug Saf 2003; 26:863–93.
62. Gill G, Swift A, Jones A, et al. Severe adrenal suppression by steroid nasal drops. J R Soc Med 2001;94:350–1.
63. Stevens DJ. Cushing's syndrome due to the abuse of betamethasone nasal drops. J Laryngol Otol 1988;102:219–21.
64. Daman Willems CE, Dinwiddie R, Grant DB, et al. Temporary inhibition of growth and adrenal suppression associated with the use of steroid nose drops. Eur J Pediatr 1994;153:632–4.
65. Findlay CA, Macdonald JF, Wallace AM, et al. Childhood Cushing's syndrome induced by betamethasone nose drops and repeat prescriptions. BMJ 1998; 317:739–40.
66. Kimmerle R, Rolla AR. Iatrogenic Cushing's syndrome due to dexamethasone nasal drops. Am J Med 1985;79:535–7.
67. Gallagher G, Mackay I. Doctors and drops. Br Med J 1991;303:761.
68. Sachanandani NS, Piccirillo JF, Kramper MA, et al. The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis. Ach Otolaryngol Head Neck Surg 2009;135:303–7.
69. Welch KC, Thaler ER, Doghramji LL, et al. The effects serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. Am J Rhinol Allergy 2010;24:26–8.