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Corticosteroids

Michelle Kapugi ▼ Kathleen Cunningham

Corticosteroids are commonly prescribed for a variety of indications due to the wide range of effects on the human body. Although they exhibit many therapeutic uses, corticosteroids are unfortunately known for their many dose- and duration-dependent toxicities. The purpose of this review is to explore indications for corticosteroid use, differences among formulations, and adverse effects and their management.

Introduction

Corticosteroids were discovered in 1935 and approved by the Food and Drug Administration in the 1950s. They are used to treat a variety of indications, are supplied in many different formulations, and have numerous effects on the human body. Because of their ubiquitous use in medicine, healthcare professionals should be well-versed in the indications, formulations, toxicities, monitoring parameters, and patient counseling points of corticosteroids.

Mechanism and Formulations

The adrenal glands synthesize and secrete the endogenous corticosteroids aldosterone and cortisol. The term "corticosteroids" is broad, encompassing all steroid hormones. Glucocorticoids, including endogenous cortisol, exhibit primarily anti-inflammatory and immunosuppressive properties. These include inhibition of the production and activity of many inflammatory cells, and redistribution to other body compartments, leading to fewer circulating immune cells overall (Ericson-Neilsen & Kaye, 2014). Mineralocorticoids, including endogenous aldosterone, influence the balance of salt and water in the body. More specifically, mineralocorticoids act on the renal tubules, leading to sodium reabsorption and potassium excretion. Although steroids are classified as mineralocorticoids or glucocorticoids, there is some overlap in the effects between classes. The relative potencies, anti-inflammatory effects, mineralocorticoid effects, and duration of action of various steroid formulations are outlined in Table 1.

Corticosteroids are readily absorbed in the gastrointestinal tract and are highly protein-bound. They undergo hepatic metabolism and renal excretion. Available corticosteroid formulations include oral, intravenous, intramuscular, intra-articular, aerosol for inhalation, and topical dosage forms. Prednisone is generally the most well-known corticosteroid and is often used as a reference point to compare with other corticosteroids. Prednisone is metabolized to prednisolone in the liver, and investigators have found better activity with administration of prednisolone than with prednisone in patients with liver disease (Madsbad, Bjerregaard, Henrisksen, Juhl, & Kehlet, 1980). Fludrocortisone has primarily mineralocorticoid activity, and because of its potassium wasting effects, it has been used in practice to control chronic hyperkalemia.

Indications

Nearly every branch of medicine uses corticosteroids to treat a variety of illnesses. They can be used at physiological doses for endocrine disorders including Addison's disease, which is characterized by adrenal insufficiency (Liu et al., 2013). Addison's disease can be precipitated by an autoimmune process or infection, leading to adrenal gland damage. Without adequate steroid replacement, patients with Addison's disease can experience adrenal crisis, which can be fatal.

When used for disorders not involving the endocrine system, corticosteroids are used at higher doses. Painful musculoskeletal disorders such as osteoarthritis use injectable corticosteroids as second-line treatment after oral options have failed. Onset of pain relief is typically quick but is unfortunately short-lived. Injections must be limited to three to four times per year per joint due to the potential for damage to the cartilage. One benefit of corticosteroid injection is the potential to remove effusions around the joint concurrently. Corticosteroids commonly used for osteoarthritis include methylprednisolone and triamcinolone. Rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematous, and psoriatic arthritis involve uncontrolled inflammatory and autoimmune processes that are commonly treated with varying doses of corticosteroids. Flares or acute worsening of symptoms typically require increased dosages of corticosteroids. Once resolved,

Michelle Kapugi, PharmD, Solid Organ Transplant PGY2 Pharmacy Resident, Northwestern Memorial Hospital, Chicago, IL.

Kathleen Cunningham, PharmD, BCPS, Assistant Professor, Pharmacy Practice, Rosalind Franklin University of Medicine & Science, Chicago, IL; and Clinical Pharmacist, Solid Organ Transplant, Residency Program Director, PGY2 Solid Organ Transplant, Northwestern Memorial Hospital, Chicago, IL.

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Table 1. Equivalent Doses, Relative Potency, and Duration of Action of Common Corticosteroids

	Approximate Equivalent Dose (mg)	Relative Glucocorticoid Activity	Relative Mineralocorticoid Activity	Duration of Action (Hours)
Hydrocortisone	20	1	1	8–12
Cortisone	25	0.8	0.8	8–12
Prednisone	5	4	0.8	12–36
Prednisolone	5	4	0.8	12–36
Methylprednisolone	4	5	0.5	12–36
Triamcinolone	4	5	0	12–36
Fludrocortisone	N/A	10	125-200	12–36
Dexamethasone	0.75	30	0	36–72
Betamethasone	0.8	25	0	>48

corticosteroid doses are gradually reduced to the lowest effective dose. Inflammatory gastrointestinal disorders including ulcerative colitis and Crohn's disease are treated with corticosteroids in various formulations such as rectal foams, enemas, and suppositories.

Severe hypersensitivity reactions are treated with corticosteroids in addition to other medications. Drugs that are known to cause infusion-related reactions, for example, rituximab, are typically given with intravenous steroids as a premedication to prevent or reduce the severity, along with diphenhydramine and acetaminophen. Topical corticosteroid creams with varying potencies can be used to treat contact dermatitis, including fluocinolone, triamcinolone, and betamethasone dipropionate.

Corticosteroids are used for solid organ transplantation as immunosuppression in combination with several other medications. They are given intravenously at high doses at the time of surgery to prevent acute organ rejection. Some transplant centers continue low doses of steroids posttransplant as a cornerstone of maintenance immunosuppression regimens, whereas other centers are "steroid-free" due to the unwanted adverse effects. In addition, corticosteroids are commonly used to treat episodes of solid organ transplant rejection.

Inhaled corticosteroids are used for chronic obstructive pulmonary disease and moderate to severe asthma for their potent anti-inflammatory effects. In addition, systemic oral steroids may be used for severe, uncontrolled asthma as a short burst for 5–10 days (Liu et al., 2013). In patients with contraindications to other available therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine, corticosteroids can be used to treat gout attacks. Corticosteroid eye drops are available to treat many inflammatory and allergy-related ophthalmological disorders.

Adverse Effects and Management

Although corticosteroids have many therapeutic benefits, they are accompanied by a multitude of adverse effects (see Table 2). Higher doses and cumulative duration of therapy are associated with an increased incidence of adverse effects. The type of adverse effects experienced and severity vary from patient to patient.

Hyperglycemia leading to worsening or development of diabetes mellitus is common. Corticosteroids cause insulin resistance, which results in patients having increased insulin requirements (Liu et al., 2013). Endocrinology referral in both the outpatient and inpatient settings may be useful in managing diabetes in patients recently started on corticosteroids or at the time of corticosteroid dosage adjustments. Blood glucose and hemoglobin A_{1c} should be monitored routinely in all patients receiving corticosteroids, and patients should be educated on the signs and symptoms of hyperglycemia, including increased thirst, urination, and blurred vision.

Table 2. Common Corticosteroid-Induced Adverse Effects Categorized by Organ System

Organ System	Adverse Effects
Cardiovascular	Fluid retention
	Hypertension
Endocrine	Hyperglycemia
	Insulin resistance
Nervous	Mood swings
	Insomnia
	Irritability
	Psychosis
Cutaneous	Red striae
	Purpura
	Skin thinning
Ophthalmological	Cataracts
	Glaucoma
Gastrointestinal	Gastric ulceration
	Esophageal ulceration
	Nausea
	Abdominal pain
Musculoskeletal	Weight gain
	Redistribution of adipose tissue
	Reduced height (pediatrics)
Immune	Immunosuppression
	Increased risk of infection

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Weight gain is one of the most frequent self-reported adverse effects and is more likely to occur with long-term steroid use (Curtis et al., 2006). In addition to increased appetite and weight gain, over time, adipose tissue is redistributed into the face, trunk, and upper back, leading to what is termed a Cushing's syndrome (Liu et al., 2013). Fluid retention can occur with all steroid formulations but is more likely with mineralocorticoids and can contribute to edema and weight gain. Weight should be monitored regularly in patients taking long-term corticosteroids.

In addition to the negative effects on cardiovascular health due to weight gain and hyperglycemia, corticosteroids have been shown to cause hypertension. One study including more than 100,000 participants found that glucocorticoids at doses of 7.5 mg or more per day of prednisone or equivalent were associated with an increased risk of hypertension (Wei, MacDonald, & Walker, 2004). Fluid retention due to the mineralocorticoid effects of corticosteroids is likely the primary factor contributing to increased blood pressure. Blood pressure should be monitored regularly and pharmacotherapy initiated when indicated. Patients should be educated to consume low salt diets to avoid the risk of additional fluid retention.

Osteoporosis is an extremely common toxicity associated with long-term corticosteroid use. Increased bone catabolism, reduced bone formation, and reduced intestinal calcium absorption lead to bone loss (Liu et al., 2013). Studies have shown an increased risk of bone fracture in patients taking long-term corticosteroids (van Staa, Leufkens, & Cooper, 2002). It is recommended that patients tawking 5 mg or more of prednisone or its equivalent per day should receive calcium and vitamin D supplementation. Bone density scanning should be assessed at baseline and regularly. Patients should be encouraged to regularly participate in weight-bearing exercises to maintain bone health.

Growth retardation has been cited as an adverse effect of corticosteroid use in the pediatric population. However, research has shown that the reduction in height is generally limited to an average of a few centimeters compared with controls and does not lead to a reduction in adult height (Peters, 2006). Parents of pediatric patients receiving corticosteroids should be counseled regarding not only the risk of stunted growth but also the low magnitude of cumulative height difference.

Neuropsychiatric effects are also possible with any duration of corticosteroid use, including insomnia, mood swings, and, in severe cases, psychosis. Morning administration of corticosteroids is recommended because of the stimulating effects that may affect sleep. Patients and family members or caregivers should be counseled on the potential for such adverse effects and should contact a healthcare professional if they occur.

Gastrointestinal adverse effects associated with the use of corticosteroids include esophageal and gastric ulceration and gastritis (Liu et al., 2013). This effect is most commonly seen when patients take concomitant NSAIDs. Corticosteroids should be taken with food to avoid gastrointestinal upset, which can include nausea and abdominal pain. Acid suppression therapies may be used for protection of the stomach if higher doses or other drugs leading to gastrointestinal adverse effects such as NSAIDs must be used concurrently, or in patients with a history of gastric ulceration. Patients should be counseled to use acetaminophen for pain control rather than NSAIDs when possible.

Ophthalmological adverse effects are also possible, including cataract formation and glaucoma development (Liu et al., 2013). Corticosteroid use causes increased intraocular pressure, leading to optic nerve damage, which can be irreversible. Patients taking long-term steroids should be seen by an ophthalmologist annually.

Cutaneous adverse effects of corticosteroids include skin thinning, purpura, and red striae (Liu et al., 2013). Impaired wound healing can occur with steroid use, which should be considered for patients undergoing major surgery. Inflammation is an important aspect of wound healing, and as potent anti-inflammatory and immunosuppressive agents, corticosteroids prevent the migration of immune cells to sites of injury, impairing the healing process. Reduced collagen production and inhibition of vascularization of wounds also contribute. In addition, the incidence of acne is increased by long-term corticosteroid use.

As corticosteroids are commonly used for their immunosuppressant effects, increased susceptibility to infection is a well-known adverse effect. A suppressed immune system makes detection of infection more difficult as fewer signs and symptoms are typically present. Opportunistic infections should be considered in immunosuppressed patients during an infectious workup. Also, in patients prescribed 16 mg or more of prednisone or its equivalent per day for 30 days or more, prophylaxis against *Pneumocystis jiroveci* pneumonia should be strongly considered (Thomas & Limper, 2004). Oral thrush can occur from inhaled corticosteroids when proper precautions are not taken. Patients using inhaled corticosteroids should be counseled to rinse the mouth and spit after use to avoid development of thrush.

A common laboratory value affected by the administration of corticosteroids is the white blood cell (WBC) count. Leukocytosis, or an elevated WBC count, is expected, especially with high doses. This is due to a process called demargination in which WBCs migrate from the endovascular lining into circulation. It is important to note that the overall number of WBCs does not increase. The phenomenon of steroid-induced leukocytosis can make ruling out infection more complicated, as leukocytosis is commonly associated with an infectious process.

Although less common, topical and inhaled corticosteroid formulations can lead to systemic adverse effects. Patients using any form of corticosteroids should be monitored carefully for potential toxicities. Because corticosteroids are used for a wide range of disorders and are available in many formulations, dosing varies greatly and is outside the scope of this review.

Withdrawal

Corticosteroid withdrawal is a serious consequence of abrupt discontinuation of therapy. Long-term corticosteroid use can lead to hypothalamic-pituitary-adrenal

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(HPA) axis suppression. This occurs due to atrophy of the adrenocortical glands after lacking the secretion of adrenocorticotropic hormone from the pituitary gland for extended periods of time (Liu et al., 2013). Symptoms can include dizziness, fatigue, nausea, arthralgia, fever, anorexia, and, in serious cases, dyspnea, hypotension, hypoglycemia, and death. Dose and duration of corticosteroid therapy are linearly related to incidence. It is recommended that patients receiving therapeutic doses (20 mg of prednisone or its equivalent per day) for 2 weeks or longer or lower doses for longer periods of time be tapered off gradually when therapy is to be discontinued. Slowly tapering off steroids allows the HPA axis to regain function. Many different steroid tapering strategies exist, and there are not currently any guideline recommendations. A reasonable strategy is to taper by 5–10 mg every week; however, some patients may require more gradual tapering regimens, and all patients should be monitored closely throughout the process.

Patient Counseling

Patients taking corticosteroids require counseling and education to avoid and manage the many adverse effects. A healthy lifestyle should be highly encouraged. A low salt diet may help reduce fluid retention, and a healthy diet along with exercise may prevent additional weight gain. Morning administration of corticosteroids with food is recommended to avoid some of the gastrointestinal and neurological effects. Patients should be counseled to not abruptly self-discontinue corticosteroids due to the potentially dangerous adverse effects associated with withdrawal.

Conclusion

Corticosteroids are essential for the treatment of numerous illnesses and disease states. Therapeutic doses vary greatly, as do the adverse effects. Patients require education on what to expect with steroid use, whether it be a short course or long-term use. Other pharmacological therapies may be necessary to counteract steroid-related adverse effects, such as gastric acid suppression, calcium and vitamin D supplementation, and opportunistic infection prophylaxis. Providers must weigh the risks versus benefits of steroid use and utilize the lowest effective dose for the least duration possible to avoid or minimize serious steroid-induced toxicities.

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