CHAPTER **30**

Steroids: Review And Update

Raymond G. Cavaliere, D.P.M.

Cortisone and related corticosteroids owe their popularity to their anti-inflammatory effect, therefore, they have become widely used and often abused in medicine. The following paper is intended to offer a review of the physiologic and pharmacologic basis of corticosteroids, as well as information on current steroids used in podiatric medicine, their side effects, indications, and contraindications.

The principal secretory products of the adrenal cortex in humans are the steroid hormones; Cortisol, Aldosterone and Androgens. Cholesterol is the precursor of all the adrenocortical steroid hormones, and itself derived from circulating low-density lipoproteins (LDL) (Fig. 1). Cortisol, a glucocorticoid, is responsible for regulating hepatic gluconeogenesis and other actions. Aldosterone, a mineralocorticoid, is responsible for sodium and potassium homeostasis, while the androgens are the sex hormones that regulate one's reproductive and behavioral characteristics.

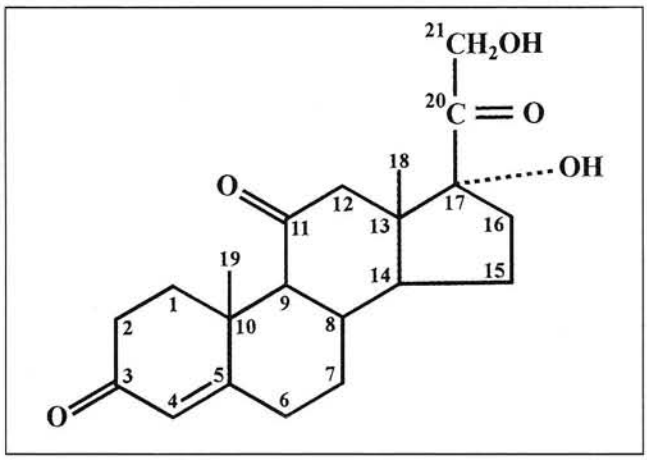

Figure 1. The structure of Cortisone. Note the cholesterol infrastructure. Other steroids are derived from changes at the various number positions.

A change in the balance of hormones in the body can have detrimental effects. One example, Cushing's syndrome, refers to the clinical picture of hypercortisolism, regardless of the pathogenesis. This may include ectopic sources (i.e., non-pituitary production of ACTH by cancers, and the therapeutic administration of large doses of synthetic, anti-inflammatory glucocorticoids). The converse to Cushing's syndrome, Addison's disease, described by Addison in the mid 19th century, includes primary failure of the adrenal cortex as well as loss of both glucocorticoid and mineralocorticoid secretory capacity.

HISTORY OF ADRENAL STEROIDS

A milestone in the history of the adrenal steroids was the report of Hench and coworkers on the effectiveness of cortisone and adrenocorticotrophic hormone (ACTH) in rheumatoid arthritis. Clinical trials in rheumatoid arthritis were dramatic with cortisone, which also provided symptomatic relief in many other disease conditions. It was recognized at that time that cortisone was not a cure, however, it seemed to provide the susceptible tissues with a shield-like buffer against the irritant.

Subsequent research on the glucocorticoids led to the development of a variety of newer steroids that have significantly greater anti-inflammatory potency than cortisone, although their influence on carbohydrate metabolism generally parallels their anti-inflammatory activity. A significant advantage of the newer steroids, such as Prednisone, Methylprednisolone (Medrol), Triamcinolone (Aristocort, Kenalog), and Dexamethasone (Decadron), is that these anti-inflammatory steroids exert little effect on renal sodium reabsorption, while still possessing potent anti-inflammatory activity.

PHARMACOLOGIC EFFECTS

Cortisol, which is the major natural glucocorticoid produced by the adrenal cortex, exerts three accurately-measurable effects and numerous miscellaneous effects. The three major effects are:

1) influence of carbohydrate, protein and fat metabolism, 2) mineralocorticoid effect, and 3) anti-inflammatory effect. Structural modifications of Cortisol can lead to a dissociation of the carbohydrate effects from the mineralocorticoid effects, thus sodium retention does not parallel the carbohydrate or anti-inflammatory effects in Cortisol derivatives. Some of the miscellaneous effects include alterations of the immune system, changes in vascular permeability, and loss of muscle integrity.

Cortisol stimulates gluconeogenesis and also tends to inhibit peripheral glucose utilization. It also causes marked accumulation of glycogen in the liver and can produce hyperglycemia and glycosuria. Therefore, Cortisol can aggravate diabetes and may bring out an insulin-resistant disturbance of carbohydrate metabolism in latent diabetics.

Cortisol promotes protein breakdown and also inhibits its synthesis. Large doses administered to children and young animals will cause failure to grow and slow healing of wounds. This failure to grow is secondary to epiphyseal growth center disturbance. Little is known about the basic action of Cortisol on fat metabolism. Unusual accumulation of fat (buffalo hump) occurs in patients treated with glucocorticoids. Glucocorticoids also have effects on water metabolism and electrolytes. Cortisone administration will result in increased sodium retention, increased potassium excretion, and hypokalemic acidosis in patients on prolonged treatment. Calcium metabolism is also affected by Cortisol. It promotes renal excretion of calcium, and may reduce calcium absorption from the intestine.

Most of the clinical uses of the corticosteroids centers around their ability to inhibit the inflammatory process. The mechanism of the anti-inflammatory action of the glucocorticoids remains unknown, but multiple theories persist: 1) suppression of migration of polymorphonuclear leukocytes, 2) suppression of reparative processes and function of fibroblasts, and 3) reversal of enhanced capillary permeability and lysosomal stabilization. Cortisone-like steroids also exert a striking effect on the number of circulating eosinophils. They may disappear from the blood following glucocorticoid administration. In addition, cortisone produces a marked decrease in circulating lymphocytes and an involution of lymphoid tissue. There are central nervous system effects such as euphoria and other behavioral abnormalities. Glucocorticoid treatment may lower convulsive threshold, while prolonged use of glucocorticoids can cause proximal muscle wasting and weakness.

The effects of corticosteroid treatment on infection are quite complex. Very large doses in animal experiments suggest an adverse effect on infection course, especially in fungal diseases. With reasonable doses, antibody production is not decreased, opsonins remain normal, and leukocytes ingest and destroy microorganisms.

Adverse effects of excessive doses of glucocorticoids after prolonged administration include: Cushing's disease, moon face, hirsutism, acne, amenorrhea, osteoporosis, muscle wasting, variable hypernatremia and hypokalemia, hypertension, aggravation of diabetes mellitus, necrotizing arteritis in rheumatoid patients, aggravation of peptic ulcer disease, psychotic manifestations, and adrenal atrophy (Tables 1, 2).

Table 1

SYSTEM-SPECIFIC SIDE EFFECTS OF ANTI-INFLAMMATORY CORTICOSTEROID THERAPY

Endocrine-Metabolic
- Hyperglycemia, including hyperosmolar non-ketotic stupor/coma and, rarely, diabetic ketoacidosis
- Truncal obesity, enlargement of cervical, supraclavicular, and mediastinal fat pads
- Retarded somatic growth (pediatric patient population)
- Acne
- Hirsutism
- Negative nitrogen and calcium balances
- Sodium retention (except with synthetic 16 substituted, 9 alpha-fluorinated corticosteroids)

Cardiovascular System
- Hypertension

Gastrointestinal Tract
- Pancreatitis
- Peptic ulcer disease

Musculoskeletal System
- Osteoporosis
- Aseptic necrosis of femoral and humeral heads
- Myopathy

Nervous System
- Pseudotumor cerebri
- Mood disorders, including both euphoria and depressive states
- Psychosis

Host Defenses Against Infectious Agents
- Increased susceptibility to opportunistic infections, owing to impaired cellular and humoral responses

Eye
- Posterior subcapsular cataract

The ultimate pharmacologic effect of glucocorticoids is dependent on the dose of the agent, type of disease to be treated, clinical status of the patient (age, gender, renal and hepatic function), and the interaction of these factors with the specific steroid administered.

Additional local effects of injected steroids include telangiectasias, hypopigmentation of the skin (sometimes resolving spontaneously), corticosteroid-induced avascular necrosis of bone, as well as local tissue atrophy. These changes can be detrimental within the foot. Injection of a steroid within the foot should therefore be deep within the tissues being treated, except in cases of scar treatment to promote fibrinolysis. Steroids injected in or around tendons can be responsible for weakening of the tendon, ultimately resulting in rupture.

Steroids should generally be used with caution around tendons of the foot and ankle, and it is recommended that a period of casting be employed after their use. Intra-articular steroids can have detrimental effects on articular cartilage with prolonged use. Soluble steroids (phosphate solution, i.e. Decadron phosphate) are perhaps better utilized in this area, as opposed to non-soluble alternatives (acetate suspension, i.e. Kenalog).

CLINICAL USES OF STEROIDS

Orally, steroids are rapidly and completely absorbed from the GI tract. After oral administration, maximal plasma concentrations are reached in one to two hours. Hepatic degradation leads to a fairly rapid fall in plasma levels, so that after eight hours only 25% of the peak value can be demonstrated, and the active drugs disappear completely in about 12 hours. Oral therapy can be useful for hypersensitivity or allergic type reactions. Methylprednisolone is available in a convenient dosing package, as Medrol Dosepak, and delivers methylprednisolone in a daily decreasing dose.

Steroids such as Hydrocortisone, Methylprednisolone, Prednisolone, and Dexamethasone, which are formulated as sodium phosphate or sodium succinate salts, exhibit rapid rates of absorption owing to increased water solubility. They are used when a rapid effect is desirable. The glucocorticoids that are conjugated with acetate (Prednisolone, Methylprednisolone, Cortisone,

Table 2

INCIDENCE OF MAJOR SIDE EFFECTS OF ANTI-INFLAMMATORY CORTICOSTEROID THERAPY

Complication	Incidence Range (%)	Duration of Therapy Prior To Appearance of Complication	Minimal daily Dose Reported To Result in Complication	Reversibility
Diabetes Mellitus	2-28	Days to months	7.5 mg prednisone	Yes
Redistribution of body fat	13	2 months	4-12 mg triamcinolone	Variable
Hypertension	4-25	2 weeks	7.5 mg prednisone	Yes
Peptic ulcer disease	0-14	1 month		Yes
Aseptic necrosis of bone	1-10	6 weeks	5-20 mg prednisone	No
Myopathy	10	1 week	10 mg prednisone	Yes
Psychiatric disorders	1-18	Days	60 mg hydrocortisone	Yes
Cataract	4	2 months	5 mg prednisone	No

Dexamethasone, and Hydrocortisone) or Acetonide Esters (Triamcinolone), demonstrate an enhanced lipid solubility resulting in a *slower* rate of absorption and prolonged duration of action. For example, a single intramuscular injection of Triamcinolone Acetonide (Kenalog-40) is absorbed slowly with effects lasting a few weeks. Lipid soluble Ester formulations are inappropriate steroid selections when a rapid clinical response is required following steroid injection. Celestone Soluspan, a mixture of betamethasone sodium phosphate and betamethasone acetate is an example of a long and short acting steroid combination. Dexamethasone, a commonly used injectable steroid is available as the short acting steroid, Decadron injectable, or as a long acting steroid, Decadron-LA.

Intra-articular steroid use can deliver a temporary or prolonged effect (with delayed systemic absorption) on the inflamed joint space. This depends on whether crystalline or non-crystalline suspensions are used. Long-term steroid utilization within joints can result in articular cartilage damage. Intra-articular use of the longer acting steroids is probably best avoided due to their lack of water solubility.

Table 3 lists a comparison of the pharmacokinetics and potencies of a variety of corticosteroids commonly used. This table will allow one to understand relative potency in terms of glucocorticoid and mineralocorticoid activity, plasma and tissue half life, as well as equivalent dosing. It should be noted that equivalent dosages are approximate and apply only to oral or intravenous administration. Potency will vary significantly when agents are administrated intramuscularly or into a joint space.

Table 3

COMPARISON OF PHARMACOKINETICS AND POTENCIES OF CORTICOSTEROIDS

Corticosteroid	Plasma (minutes)	Tissue (hours)	Relative Potency		Equivalant Dose (mg)
			Glucocorticoid Activity	Mineralocorticoid Activity	
Cortisol (hydrocortisone)	90	8-12	1	1	20
Cortisone (11-dehydrocortisol)	30	8-12	0.8	0.8	25
Prednisone	60	12-36	4	0.8	5
Prednisolone	200	12-36	4	0.8	5
6 alpha-methylprednisolone	180	12-36	5	0.5	4
Fludrocortisone (9 alpha-fluorocortisol)	200	8-12	10	125	–
Triamcinolone (9 alpha-fluoro-16 alpha-hydroxyprednisolone)	300	12-36	5	0	4
Betamethasone (9 alpha-fluoro-16 beta-methylprednisolone)	100-300	36-54	25	0	0.75
Dexamethasone (9 alpha-fluoro-16 alpha-methylprednisolone)	100-300	36-54	25	0	0.75

CONTRAINDICATIONS TO THE USE OF STEROIDS

Relative contraindications to high-dose anti-inflammatory steroid use are the presence of bacterial infection, poorly-controlled diabetes mellitus, and advanced demineralizing bone disease. Peptic ulcer disease would also be considered to be a relative contraindication.

CONCLUSION

Steroids have a variety of uses within the foot and ankle. Their use centers mainly around their potent anti-inflammatory effects and their use as fibrinolytics. There are many potential side effects, which can affect many body systems. An understanding of steroid administration and pharmacokinetics will enhance their effective use, and help avoid potential complications. Steroids require close monitoring, and the smallest dose should be used over the shortest amount of time to avoid potential toxicity. Armed with this information, the physician is able to make more intelligent choices when utilizing a steroid within the clinical practice.

BIBLIOGRAPHY

Goodman and Gillman: The Pharmacological Basis of Therapeutics, 8th Ed, Elmsford, NY, Pergmon Press, 1990.

Hench PS, Shocumb CH, Barnes AR, Smith HL, Polley HL, Kendall EC: The Effects of Adrenal Cortical Hormone 17-Hydroxy-11-Dehydro=Corticosterone (Compound E) On the Acute Phase of Rheumatic Fever, Mayo Clinic Proceedings #24:277, 1949

Hench PS: Introduction: Cortisone and ACTH in Clinical Medicine, Mayo Clinic Proceedings #25: 474, 1950

Goth A: Medical Pharmacology, 9th Ed, St. Louis, Mo, Mosby Yearbook, 1978.