Perioperative Implications

Preoperative Concerns

- Deficiency may cause megaloblastic anemia especially in the setting of chronic alcohol intake and medications that inhibit dihydrofolate reductase (i.e., methotrexate, trimethoprim).
- Consider general nutritional status (i.e., if evidence of poor diet, folic acid deficiency likely).
- Consider specific underlying conditions (i.e., anorexia, alcoholism, malabsorption disorders).
- Continue periop supplementation as needed.

Induction/Maintenance

- Same as Preoperative Concerns.
- Avoid repeated use of N_2O.

Adjuvants/Regional Anesthesia/Reversal

- Same as Preoperative Concerns

Postoperative Period

- Same as Preoperative Concerns

Anticipated Problems/Concerns

- Rare allergic reactions, especially to parenteral formulation.
- Generally none in otherwise healthy pts.
- May counteract the antiepileptic effect of phenytoin, phenobarbital, and primidone at high doses (>15 mg/d), leading to seizures.
- Potential danger of mistreating pt with vitamin B_{12} deficiency with folic acid; may result in improvement of megaloblastic anemia, but neurologic deficits of vitamin B_{12} deficiency may progress and become irreversible.

Glucocorticoids

Amit Prabhakar | Alan David Kaye

Uses

- Used to treat a wide range of illnesses including but not limited to autoimmune disorders, postop nausea and vomiting, and chronic pain

Overview/Pharmacology

- Adrenal cortex produces and releases two different types of corticosteroids: Mineralocorticoids (maintain salt and fluid balance) and glucocorticoids (affect metabolism and inflammation).
- Glucocorticoids have significant, wide-ranging physiologic effects by binding to cell surface receptors and crossing cell membranes to modify genetic expression.
- Endogenous glucocorticoids include cortisol.
- Exogenous glucocorticoids include prednisone, prednisolone, triamcinolone, dexamethasone, and betamethasone.

Physiology

- Glucocorticoids play a pivotal role in normal body physiology and the stress response.
- Three major mechanisms control cortisol release:
  - Negative feedback via the HPA axis: ACTH from the anterior pituitary stimulates the secretion of cortisol from the adrenal cortex. Cortisol exerts a direct negative feedback effect on ACTH secretion.
  - Diurnal variation: Cortisol is secreted in pulses that follow a circadian rhythm dependent on pt's sleep-wake pattern. Cortisol levels are highest in the morning, upon awakening, and lowest in the evening.
- Stress: Physical (trauma, surgery, exercise), psychologic (pain, anxiety), or physiologic (nausea, fever) stress can override the negative feedback mechanisms and lead to a rapid increase of cortisol concentration.
- Metabolic effects:
  - Stimulation of gluconeogenesis by the liver, resulting in increased blood glucose
  - Mobilization of fatty acids from adipose tissue and enhanced fatty acid oxidation in cells
  - Decreased protein synthesis and catabolism of proteins in cells
- Anti-inflammatory activity: Potent anti-inflammatory activity via inhibition of phospholipase A2 and COX-2. Blunts production and cascade of inflammatory cytokines.
- Bone metabolism: Inhibit osteoblast function. Excess results in osteopenia and osteoporosis.
- Blood pressure: Affects the kidney and vasculature to increase blood pressure; increases sensitivity of vascular smooth muscle to catecholamines and angiotensin II.
- CNS: Plays a role in depression, euphoria, apathy, and lethargy.
- Fetal development: Maternal cortisol plays key role in the fetal production of pulmonary surfactant and in the expression of key hepatic enzymes.
- Other endocrine effects: Suppresses thyroid axis; inhibits GnRH, LH, and FSH.

Commonly Used Types

- Exogenous corticosteroids have varying degrees of potency, duration of action (DOA), and mineralocorticoid or glucocorticoid activity.
- Cortisol: Equal anti-inflammatory and mineralocorticoid activity; short DOA (<12 h)
- Cortisone: Equal anti-inflammatory and mineralocorticoid activity; short DOA
- Prednisone: Anti-inflammatory > mineralocorticoid activity; intermediate DOA (12–36 h)
- Prednisolone: Anti-inflammatory > mineralocorticoid activity; intermediate DOA (12–36 h)
- Triamcinolone: Anti-inflammatory only; no mineralocorticoid activity; intermediate DOA (12–36 h)
- Dexamethasone: Potent anti-inflammatory only; no mineralocorticoid activity; long DOA (>36 h)
- Betamethasone: Potent anti-inflammatory only; no mineralocorticoid activity; long DOA (>36 h)
- Fludrocortisone: Potent mineralocorticoid activity

Relative Potency of Commonly Utilized Agents

- Anti-inflammatory potency: Cortisol 1, triamcinolone (Aristocort) and 6-methylprednisolone (Depo-Medrol) 5, fludrocortisone 10, betamethasone (Celestone) 25
- Mineralocorticoid potency: Cortisol 1, fludrocortisone 10
- Equivalent dose, mg: Cortisol 20, triamcinolone (Aristocort) and 6-methylprednisolone (Depo-Medrol) 4, betamethasone (Celestone) 0.75

Pathology

- Adrenal overactivity
  - Cushing syndrome: Due to excess cortisol in the body.
  - Cushing disease: Due specifically to ACTH-producing pituitary adenoma. Hypercortisolemia manifests as obesity, thin extremities, hypertension, buffalo hump, easy bruising, abdominal striae, hypervolemia, hypokalemic metabolic acidosis, osteoporosis, osteopenia, moon facies, poor wound healing.
- Adrenal insufficiency:
  - AD: Primary adrenal insufficiency. Pts with AD usually lack both mineralocorticoid and glucocorticoid production. Symptoms include weakness, weight loss, postural hypotension, constipation, diarrhea, anorexia, hyperpigmentation, hypoglycemia, hyperkalemia, and hyponatremia. AD usually has an autoimmune etiology but can also be due to tuberculosis, cancer, or amyloidosis.
  - Secondary adrenal insufficiency: Lack of ACTH production from the anterior pituitary. Can be due to abrupt cessation of exogenous steroids or surgical removal of a pituitary adenoma.
  - Adrenal crisis: Sudden, severe worsening of adrenal insufficiency. Manifests as severe dehydration, vomiting, diarrhea, hypotension, convulsions, and/or loss of consciousness.
- Adverse effects of steroid supplementation:
  - Short term: Exacerbation of Htn, fluid retention, stress ulcers, psychologic disturbances, osteoporosis, delayed wound healing, increased susceptibility to infection, decreased glucose tolerance. Nonparticulate steroids are recommended over particulate steroids for epidural steroid injections due to risk of intravascularly mediated embolization.
  - Long term: Suppression of the HPA axis, hypokalemic metabolic acidosis, weight gain, redistribution of body fat, proximal skeletal muscle wasting
  - Fungal meningitis: Outbreak (753 total infections in 20 states, 2012–2013) and mortality (64 deaths over the same time period) related to steroid compounds manufactured at the New England Compounding Center, a compounding pharmacy that was neither licensed nor inspected by USA FDA for large-scale pharmaceutical manufacturing.

Assessment Points

System	Effect	Assessment by Hx	PE
HEENT			Dilated, reactive pupils
CV	Retention of sodium and free water	Palpitations Sweating Hyponatremia	Htn/hypotension Tachycardia Autonomic degeneration including: loss of R-R variability on ECG
RESP	No consistent changes	COPD, asthma	Tachypnea, apnea
GI	Abdominal pain, gastritis	IBD, GI ulcer	Abdominal discomfort, guarding
ENDO	Insulin resistance induced hyperglycemia	DM	Sensory deficits from neuropathy
CNS/MS	Euphoria, panic attacks Inhibit calcium absorption Anxiety, mood disorders Hallucinations Sleep disturbances	Cataracts Osteoporosis	Altered mental status Muscle weakness Pathologic fractures Tremors, delirium
DERM		Bruising	Skin changes

Key References: Ericson-Neilsen W, Kaye AD: Steroids: pharmacology, complications, and practice delivery issues, *Ochsner J* 14(2):203–207, 2014; Shaikh S, Verma H, Yadav N, et al.: Applications of steroid in clinical practice: a review, *ISRN Anesthesiol* 2012(7), 2012.

Perioperative Implications

- Special consideration of preop blood glucose and lytes
- Steroid supplementation is necessary in the periop setting if pts have a history of hypoadrenocorticism or suppression of the HPA axis due to a history of steroid intake.
- In presence of adrenal insufficiency, it is important to be hypervigilant to prevent precipitation of adrenal crisis secondary to surgical stress.
  - Preop management should include treatment of hyperkalemia, hyponatremia, and hypovolemia.
  - Stress dose of glucocorticoids (100 mg hydrocortisone phosphate IV) should also be given
  - Avoid medications that are inhibitors of cortisol synthesis. These include ketoconazole, aminoglutethimide, etomidate (selectively inhibits adrenal 11-beta hydroxylase).
- Cushing disease or syndrome:
  - Obese/morbidly obese pts: May present difficult airways; carefully assess Mallampati and TM distance.
  - Pituitary adenoma can result in increased ICP.
  - Use opiates to prevent sympathetic surge associated with intubation.
  - Avoid ketamine to prevent excessive sympathetic effects.
  - Etomidate may be used.

Gold (Auranofin, Aurothioglucose, Aurothiomalate)

Kevin Miller | Jonathan Gavrin

Uses

- Rheumatoid arthritis treatment for patients without sufficient response to initial treatment with NSAIDs, steroids, or other DMARDs.
- May have efficacy in pemphigus vulgaris, psoriatic arthritis, and palindromic rheumatism but lacks trials is and rarely used due to availability of other therapies.
- Availability of other DMARDs, such as biologic TNF inhibitors and methotrexate, has decreased the use of gold.

Perioperative Risks

- IM gold associated with higher dropout rates due to side effects when compared to other DMARDs (up to 19% in one study).
- Cutaneous reactions range from erythema and pruritus (30% of pts) to exfoliative dermatitis.
- Mucous membrane lesions (20% of pts), including stomatitis, pharyngitis, gastritis, and colitis.
- Dermal deposits and chrysiasis (gray-to-blue pigmentation of sun-exposed skin) are possible with large cumulative doses. Effect on transcutaneous Hgb saturation measurement is unknown. Some pts are noted to have corneal deposits.
- Allergic (5% of pts): Anaphylactoid and nitritoid reactions, with transient flushing, nausea, hypotension, dizziness, and diaphoresis (especially seen in pts also taking ACE inhibitors).
- GI (5% of pts): Diarrhea (common in pts taking the oral formulation auranofin), enterocolitis, jaundice and hepatic toxicity (from cholestasis), transaminitis, pancreatitis, and metallic taste.
- Renal: Proteinuria (10–15%, usually resolves with cessation of treatment), renal tubule deposition, acute renal failure, and nephrotic syndrome. Use caution in pts with decreased renal function due to delayed elimination.
- Pulmonary infiltrates and interstitial pulmonary disease are rare and usually resolve with cessation of treatment; difficult to differentiate from underlying RA pulm fibrosis.
- Hematologic: Thrombocytopenia (<5%, usually develops in first 6 mo, immune-mediated attack on bone marrow reverses with cessation of treatment), leukopenia (2%), eosinophilia, bone marrow suppression, rare progression to aplastic anemia. This can be avoided in pts given antimalarials, phenylbutazone, or oxyphenbutazone because of cumulative bone marrow suppression.
- Neurologic: Cranial nerve palsies, encephalitis, Guillain-Barré-like syndrome. Peripheral neuropathy (<1%—painful paresthesias progressing to asymmetric weakness, may be preceded by fever/rash; direct toxic effect vs. hypersensitivity reaction).
- Not usually administered to pregnant pts but limited published data are available.
- Use caution in the elderly (due to underlying renal insufficiency and bone-marrow suppression).

Overview/Pharmacology

- Consider IM (aurothioglucose, aurothiomalate) versus oral (auranofin) use. Monitor closely for side effects; oral administration has less common side effects but higher incidence of immunosuppression and rare side effects.
- Rapidly absorbed; peak serum concentrations after IM injection 2–4 h.
- Highly (~95%) albumin-bound and also binds to macroglobulins.
- Slow elimination, with half-life of single 50-mg dose IM approximately 7 d.
- Can be noted in tissues up to 20 y following the last dose.
- After IM full dose, blood levels return to normal in 40–80 d.
- Elimination: Majority occurs in renal (approximately 75%), with the remainder in feces.

Drug Class/Mechanism of Action/Usual Dose/Monitoring

- Anti-inflammatory DMARD.
- Free thiol group may contribute to reduction in oxidative stress.
- Gold compounds sequestered in phagocytic cells of reticuloendothelial system (liver, spleen, lymph nodes) and synovial membranes.
- Gold suppresses migration of monocytes and macrophages.
- Suppresses proinflammatory cytokines such as interleukins 1α, 1β and 6, TNF-α, as well as prostaglandin synthesis, C1 inhibition, lysosomal hydrolytic enzymes and elastase inhibition, and B-cell inhibition.
- Slows radiologic progression of RA.
- Initial dose of 10 mg, with 25 mg dose in a wk used to test for hypersensitivity.
- Subsequent doses totaling 50 mg per wk are given until 1 g reached. May not see clinical effect for up to 20 wk.
- Continuing therapy involves 50 mg IM every 2–6 wk.
- Monitor for anemia, leukopenia, and thrombocytopenia with regular blood testing and for proteinuria with urinalysis.
- Auranofin dosage initially should be 6 mg/d in divided doses; may be increased to 9 mg/d in divided doses after 6 mo.