Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Bradycardia, dysrhythmia Slight BP increase	Rare	Pulse	ECG
CNS	Extrapyramidal symptoms (rare), mania (rare), serotonin syndrome (rare)	Headache, anxiety, tremor		CK
ENDO	SIADH secretion (rare)	Confusion with significant hyponatremia, seizures	GCS	Urine specific gravity Plasma and urinary sodium
GI	Nausea, weight loss			
MS	Serotonin syndrome (rare)	Arthritic complaints (infrequent), muscle rigidity		
HEME	Impaired hemostasis			May possibly be identified with plt function testing but no specific assay for SSRI effect available

Key References: Zahajszky J, Rosenbaum JF, Tollefson GD: Fluoxetine. In Schatzberg AF, Nemeroff CB, editors: *The American Psychiatric Publishing textbook of psychopharmacology,* ed 4, Washington DC, 2009, American Psychiatric Publishing, p 289; Peck T, Wong A, Norman E: Anaesthetic implications of psychoactive drugs, *Contin Educ Anaesth Crit Care Pain* 10:177–181, 2010.

Perioperative Implications/Possible Drug Interactions

- Headache, anxiety, and nausea are common symptoms.
- May inhibit cytochrome P450 enzymes and increase serum concentrations of other drugs (beta-blockers, phenytoin, benzodiazepines, antipsychotics, tramadol) and potentiate their effects.
- Inhibition of CYP2D6 reduces conversion of codeine to morphine and may result in inadequate analgesia.
- Do not give to pregnant pts without assessing risk/benefit ratio.

Anticipated Problems/Concerns

- Approximately 7% of Caucasians lack the cytochrome P450 (CYP2D6) that probably metabolizes fluoxetine; these individuals may develop higher serum concentrations of fluoxetine and be more prone to side effects.
- Serotonin syndrome—characterized by agitation, confusion, diaphoresis, and muscle rigidity—may develop in pts who receive a combination of fluoxetine and MAO inhibitors.

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Folic Acid

Karen E. Iles | David W. Miller

Uses

- Prevention of folic acid deficiency
- Treatment of megaloblastic anemia
- Experimental treatment for major depressive disorder
- Treatment of folic acid deficiency caused by anorexia, chronic use of oral contraceptive and some antiepileptic drugs, alcoholism, malabsorption diseases (e.g., sprue), bowel resection, and diverticulosis
- Reduces incidence of neural tube defects (spina bifida) and congenital heart defects in developing fetus
- Reduces homocysteine; may have cardiovascular benefits (no evidence of such from randomized trials, but much anecdotal evidence)

Perioperative Risks

- Chronic overdosage increases proliferation of cancer as demonstrated in epidemiologic studies and in vitro studies of breast cancer.
- Exposure to nitrous oxide disrupts folic acid metabolism; repeated exposure can cause deficiency.
- Supraphysiologic doses (>15 mg/d) may decrease seizure threshold in pts taking some antiepileptic medications.

Worry About

- Allergic reactions (rare); most in response to the parenteral form.
- Loss of appetite, nausea, lethargy, stomach pain, insomnia.
- Supraphysiologic doses (>15 mg/d) increase all symptoms listed above.
- May cause seizures (>15 mg/d); higher risk in epileptic pts.

Overview/Pharmacology

- Vitamin with close synergistic relationships with vitamin B_{12}, ascorbate, and zinc.
- Very little found as folic acid in nature; converted to tetrahydrofolate in vivo.
- Absorption most efficient in the duodenum and upper jejunum.
- Loss from the body is prevented by efficient enterohepatic recirculation.
- Some fecal excretion; very little excreted in the urine.
- Alcohol decreases blood levels by interfering with enterohepatic recirculation.
- Tetrahydrofolate accepts and denotes one carbon group in amino acid degradation and metabolic reactions.

Drug Class/Mechanism of Action/Usual Dose

- Vitamin.
- Accepts and denotes one carbon group in amino acid degradation and metabolism reactions (i.e., in the synthesis of glycine from serine).
- Critical for cell division because required for purine and thymidine synthesis
- Oral and parenteral forms.
- RDA is 400 μg/d for healthy individuals and 600 μg/d for pregnant women.
- Higher requirements for anemia, antifolate drug therapy, and so on; 1 mg 1–3 times daily PO or IM or IV.
- Given as a multivitamin containing vitamin B_{12} because it can mask vitamin B_{12} deficiency and accompanying neurologic damage.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Improves O_2 delivery	Better exercise tolerance		Hgb
GI	Improves cell division	Less diarrhea	Better hydration/absorption	
ENDO/ METAB	Improves nucleic acid/protein synthesis		Weight gain	Folate level
HEME	Improves RBC synthesis	Better exercise tolerance		Hgb

Key References: Kaushansky K, Kipps TJ: Hematopoietic agents: growth factors, minerals, and vitamins. In Brunton LL, Chabner BA, Knollmann BC, editors: *Goodman & Gilman's the pharmacological basis of therapeutics,* ed 12, New York, 2011, McGraw-Hill, pp 1067–1100; Goodman BP: Metabolic and toxic causes of myelopathy, *Continuum (Minneap Minn)* 21(1 Spinal Cord Disorders):84–99, 2015.

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.