Drug Class/Mechanism of Action/Usual Dose

- EACA is an antifibrinolytic agent of the lysine analogue class.
- EACA inhibits fibrinolysis principally via inhibition of plasminogen activators and to lesser degree through antiplasmin activity.
- The optimal dosage in the setting of CPB is undefined, but the following is a commonly used regimen in adults: Initial loading dose is 5 g IV over 1 h, followed by a continuous infusion of 1 g/h; maximum recommended daily dose is 30 g.
- Plasma concentrations are increased in pts with severe renal dysfunction, but no quantitative recommendations for dosing adjustments are available.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CNS	Dizziness, confusion, delirium, headache, seizure		Neurologic exam	
CV	Hypotension, bradycardia		Vital signs	ECG
GI	N/V, diarrhea			Lytes
RENAL	Renal failure, urinary tract obstruction	Oliguria		BUN/Cr
HEME	Thrombosis	Potential causes for DIC	Evidence for paradox of simultaneous thrombosis and bleeding	CBC, PT/PTT, DIC profile
MS	Myopathy, rhabdomyolysis	Myalgia, malaise, fatigue	Muscle weakness	CPK

Key References: Franchini M, Mannucci PM: Adjunct agents for bleeding, *Curr Opin Hematol* 21(6):503–508, 2014; Ortmann E, Besser MW, Klein AA: Antifibrinolytic agents in current anaesthetic practice, *Br J Anaesth* 111(4):549–563, 2013.

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns

- In the presence of hematuria originating in the upper urinary tract, EACA can cause intrarenal obstruction due to clot retention.

Drug Interaction

- EACA should not be administered to pts treated with factor IX complex or antiinhibitor coagulant complex unless the risk of thrombosis is outweighed by the potential benefit of EACA.

Induction/Maintenance

- Close hemodynamic monitoring of cardiac pts because of the risk of hypotension and sinus bradycardia, particularly with rapid IV administration and in hypovolemia.
- Monitor renal function in pts with renal dysfunction and consider dosage adjustments depending on clinical response and degree of renal function impairment.
- Consider transfusion of platelets, FFP, and cryoprecipitate in the presence of bleeding not caused by hyperfibrinolysis.

Postoperative Period

- Continue assessment of bleeding and monitoring of coagulation profiles after discontinuation of EACA therapy.

Anticipated Problems/Concerns

- EACA should not be administered without a definite diagnosis and/or lab finding indicative of hyperfibrinolysis (hyperplasminemia) because of the potential for thrombotic complications in pts with DIC and underlying hypercoagulable states.

Fluoxetine (Prozac)

Stephen J. Shepherd

Uses

- Fluoxetine, an SSRI, is one of the most commonly prescribed medications in USA.
- Prescribed for the treatment of depression, OCD, and bulimia nervosa.

Perioperative Risks

- May be associated with periop anxiety
- Drug interactions with beta-blockers, phenytoin, benzodiazepines, antipsychotics (may increase levels by inhibition of CYP2D6), tramadol, and codeine

Worry About

- Suicidal behavior, psychotic, or extrapyramidal reactions (rare).
- Serotonin syndrome with concomitant administration of MAO inhibitors, tricyclic antidepressants, antipsychotics, tramadol, or meperidine.
- Increased risk of abn bleeding, particularly if combined with vit K antagonists or NSAIDs.
- Potential for increased mortality in high-risk pts, although whether there is a causative association or observation is unknown.

Overview/Pharmacology

- Selective inhibitor of serotonin reuptake.
- Administered as racemic mixture of R- and S-enantiomers.
- S-enantiomer more potent than R-enantiomer.
- Active metabolites, R- and S-norfluoxetine, formed by demethylation.
- Eliminated mainly through oxidative metabolism and conjugation.
- Long elimination $T_{½}$: 1–10 d for fluoxetine, 3–20 d for norfluoxetine.
- Fluoxetine inhibits (and is probably metabolized by) liver cytochrome P450 enzymes CYP2D6 and possibly CYP3A4: May inhibit metabolism, increase levels of beta-blockers, benzodiazepines, antipsychotics; similarly may decrease conversion codeine to morphine.
- Serotonin promotes platelet activation and vasoconstriction following vascular injury. Platelets cannot synthesize more, hence SSRIs deplete intracellular levels and impair hemostasis; opinions differ as to clinical relevance of this.
- Difficult to establish relationship between plasma concentration of fluoxetine and its effect, probably because there are four active compounds (R- and S-fluoxetine and R- and S-norfluoxetine) that require separate measurement.
- Withdrawal may cause dizziness, GI upset, and confusion/delirium, particularly periop.

Drug Class/Mechanism of Action/Usual Dose

- Selective inhibitor of serotonin reuptake are taken chronically for moderate to severe depression, OCD, bulimia nervosa, PTSD, and hypersexuality (off label).
- Full antidepressant effect may be delayed until 4 wk of treatment or longer
- Initial dose PO: 20 mg/d.
- Maximal dose: 80 mg/d.
- Alternatives: Other antidepressant medications, psychotherapeutic intervention.

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.

Acknowledgment

The author wishes to acknowledge the contribution of Dr. Donald D. Koblin to the previous edition of this chapter.

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.