Diuretics

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Uses

- Prescribed for pts with Htn, CHF, elevated ICP, edema, hemoglobinuria, low intraop UO, hyperkalemia, volume overload, and rhabdomyolysis.
- Mannitol may function as a renal preservative by free radical scavenging and toxin dilution.
- Fenoldopam is a selective dopamine-1 agonist. As a vasodilator, it lowers blood pressure and augments renal blood flow, which improves UO and glomerular filtration rate. It may also serve as a renal protectant. Usual dose begins at 0.03 μg/kg/min titrated to effect.
- HCTZ is used to treat hypercalcemia for kidney stones.

Perioperative Risks

- Hypokalemia
- Hypovolemia
- Low intraop UO
- Hyperkalemia with aldosterone antagonists
- Hypomagnesemia

Worry About

- Hypokalemia and hypovolemia.
- Low intraop UO if preop holds usual diuretics.
- Hypokalemia provoking and/or aggravating digitalis toxicity.
- Deafness with ECA and tinnitus with furosemide.
- End result of diuretic use is increased UO with net loss of H_2O and solutes, especially K^+ and Mg^{2+}.
- Onset of diuresis is within 10 min after IV administration.
- With the exception of an aldosterone antagonist and K^+-sparing diuretics, all others cause K^+ loss.
- Serum K^+ <3.5 mEq/L in 15% of pts and <3.0 mEq/L in up to 10% of diuretic-treated pts.
- Chronic diuretic-induced hypokalemia is less arrhythmogenic than acute, but serum K^+ <3.0 mEq/L is associated with a twofold greater incidence of ventricular arrhythmias than K^+ >3.0 mEq/L.
- Site-specific action associated with additional effect if diuretics from two classes used.
- Mannitol causing brief but appreciable hypervolemia risking CHF and ICP if bolused.
- Mannitol causing hypotension from high osmolar effect if given too rapidly.

Drug Class/Mechanism of Action/Usual Dose

- Diuretics belong to osmotic, carbonic anhydrase inhibition, benzothiadiazide, high-ceiling (loop), K^+-sparing, or aldosterone antagonist class of drugs, based on mechanism of action.
- Only osmotic and loop diuretics are used intraop.
- Osmotic diuretic: Mannitol—ascending loop, limits H_2O reabsorption; onset of action 5–15 min after IV dose: renal clearance
- Usual dose: Mannitol 0.25–2 g/kg (rapid bolus may precipitate hypotension)
- Loop diuretics: Ascending loop, limit NaCl reabsorption; onset of action 5 min after IV dose; $T_{½}$ 1–2 h; duration of action 3–6 h: renal clearance
- Usual IV dose for 70-kg person: Furosemide: 5–40 mg (0.1–1.0 mg/kg); ECA: 25–50 mg (0.5–1 mg/kg); bumetanide: 0.5–1 mg q 2–3 h; max 10 mg/d
- Furosemide PO to IV conversion 2:1

Drug Effects

System	Effect
HEENT	Transient (<24 h) deafness or vertigo may follow IV rapid bolus of ECA; less common after furosemide or bumetanide; rarely permanent. Tinnitus may follow furosemide.
CV	Transient increased in venous capacitance causes hypotension with rapid IV loop diuretic administration; acute transient increase in intravascular volume precedes diuresis with mannitol; vasodilation with fenoldopam.
ENDO	Hypokalemia, metabolic alkalosis
GU	Diuresis
CNS	Mannitol decreased ICP following transient increase; the latter may be mitigated by coadministration of furosemide.

Key References: Bebawy JF, Ramaiah VK, Zeeni C, et al.: The effect of furosemide on intravascular volume status and electrolytes in patients receiving mannitol: an intraoperative safety analysis, *J Neurosurg Anesthesiol* 25(1):51–54, 2013; Kheterpal S, Khodaparast O, Shanks A, et al.: Chronic angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy combined with diuretic therapy is associated with increased episodes of hypotension in noncardiac surgery, *J Cardiothorac Vasc Anesth* 22(2):180–186, 2008.

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns

- In chronic hypertensive pts treated with diuretics, a significant intravascular volume contraction may exist, making them more prone to hypotension following induction of anesthesia and any acute blood loss.
- Hypokalemia: Check serum K^+; consider enhanced digitalis toxicity.
- Hypomagnesemia is common in pts treated with loop or thiazide diuretics and predisposes them to ventricular arrhythmias. It should be suspected when hypokalemia is noted. Hypomagnesemia should be corrected prior to repleting K^+.
- Enhanced ototoxicity and nephrotoxicity of loop diuretics are associated with rapid administration of large IV doses and concurrent use of another nephrotoxic drug (e.g., aminoglycoside antibiotic, another loop diuretic, and some cephalosporins, especially cephaloridine).
- It is probably best to continue a chronic dose through the periop period, including day of surgery. (UO will decline if a diuretic not given on day of surgery.) No increase in hypotension will be seen if usual oral diuretics are given preop the day of surgery.

Induction/Maintenance

- Intraop loop diuretic use may significantly decrease serum K^+ level with diuresis.

Adjuvants

- Enhanced renal clearance of other drugs (e.g., neuromuscular-blocking agents) provoked by diuresis is not clinically problematic.

Anticipated Problems/Concerns

- Pts receiving diuretics preop should be considered volume contracted until proven otherwise.
- Hypokalemia associated with diuresis will be aggravated by hyperventilation, which further lowers serum K^+ an additional 0.5 mEq/L for each 10 mm Hg decrease in $PaCO_2$.
- Catecholamine β effect (endogenous and/or exogenous); also lowers serum K^+.
- Low intraop UO in a euvolemic pt if antidiuretic hormone/stress mediated will, in authors' experience, respond to very low dose (e.g., 2–5 mg furosemide) with increased UO.

Epsilon-Aminocaproic Acid (Amicar)

Frank W. Dupont

Uses

- EACA is a hemostatic agent used in the treatment of hyperfibrinolysis associated with excessive bleeding.
- Indications: Fibrinolytic bleeding associated with surgical complications following heart surgery (with or without CPB) and portacaval shunt; surgical hematuria (following prostatectomy and nephrectomy) or nonsurgical hematuria (accompanying polycystic or neoplastic diseases of the GU system); acute and life-threatening abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix; hematologic disorders such as amegakaryocytic thrombocytopenia
- Methods of administration: IV solution, oral solution, tablets

Perioperative Risks

- Increased risk of developing thrombosis in pts, who are concurrently treated with factor IX complex or antiinhibitor coagulant complex

Worry About

- EACA should not be used when there is evidence of an active intravascular clotting process. When there is uncertainty as to whether the cause of bleeding is primary fibrinolysis or DIC, this distinction must almost certainly be made before administering EACA. EACA must not be used in the presence of DIC without concomitant heparin.

Overview/Pharmacology

- EACA is an inhibitor of fibrinolysis and enhances hemostasis when fibrinolysis contributes to bleeding.
- Renal excretion is the primary route of elimination: 65% is eliminated unchanged within 12 h; approximately 11% is metabolized; renal clearance is 116 mL/min; and terminal elimination half-life is approximately 2 h.

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.