Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Mydriasis		Eye exam	
GI	Nausea Vomiting Dyspepsia			Endoscopy
ENDO	Pancreatitis	LUQ abdominal pain radiating to the back	Abdominal pain with palpation	Glucose, AST, ALT, CT, MRI, ERCP, endoscopic (US)
HEME	Agranulocytosis Thrombocytopenia Aplastic anemia	Epistaxis Easy bruising	Hematoma Petechiae	Coagulation factors, fibrinogen, plt count, bleeding time, PT, PTT, vWF level, TEG
HEPAT	Hepatocellular toxicity, Alpers-Huttenlocher syndrome (especially in pts <2 y of age)	Nausea Anorexia Bleeding	Hepatomegaly Biopsy exam for microvesicular steatosis, severe hepatocellular necrosis Fever, rash, lymphadenopathy, peripheral eosinophilia, coagulopathy	LFT, liver biopsy, PT/INR
DERM	Stevens-Johnson syndrome Alopecia Rash			
RENAL	Hyperammonemic encephalopathy	Acute onset of impaired consciousness, focal neurologic symptoms, increasing seizure frequency	Encephalopathy	Urea levels Ammonia levels
CNS	Tremor, somnolence, potentiates depressive effects of ETOH			Blood alcohol level
OTHER	Teratogenicity weight gain, growth plate ossification Peripheral edema			Albumin level

Key References: Abdallah C: Considerations in perioperative assessment of valproic acid coagulopathy, *J Anaesthesiol Clin Pharmacol* 30(1):7–9, 2014; Perks A, Cheema S, Mohanraj R: Anaesthesia and epilepsy, *Br J Anaesth* 108(4):562–571, 2012.

Perioperative Implications

Preoperative Concerns

- History of concomitant bleeding diathesis.
- Obtain laboratory coagulation tests (coagulation factors, fibrin formation, fibrinogen, platelet count, bleeding time, PT, PTT, vWF level, TEG, LFT) when considerable blood loss is anticipated.
- Bleeding risk reversed with dose reduction or cessation.
- If anticipating blood loss, prepare platelets, blood products, and DDAVP.
- Performance of neuraxial anesthesia must be made on an individual basis.
- Continue periop and resume immediately postop for risk of seizure.
- Assess neuropsychiatric status.
- Review for other AEDs or other drug interactions with valproate.
- Increased sedation in elderly and with EtOH and/or benzodiazepine use.

Induction/Maintenance

- Anticonvulsants may stimulate hepatic microsomal enzymes, thus increasing the rate of biotransformation of volatile halogenated agents and posing increased risk of organ toxicity.
- Consider EEG.
- Mildly exaggerated effects of thiopental, propofol, benzodiazepines.

Adjuvants/Regional Anesthesia/Reversal

- Risks of neuraxial anesthesia must be reviewed on an individual basis in terms of bleeding history.
- Possible delayed emergence with GA.

Anticipated Problems/Concerns

- Screen for coagulopathy in pts on long-term valproate or multiple AEDs.
- With neuraxial anesthesia, risk of bleeding may be increased.
- May displace protein-bound drugs (warfarin, methotrexate, sulfonylurea, thiopental), thus augmenting drug's effect.

Vitamin B_{12} (Cyanocobalamin)

John K. Stene

Indications

- Incidence of deficiency in USA varies with age: 5% of those <55 y, 10% of those 55–64 y, 10–15% of those 65–74 y, and 24% of those 74–80 y old. Some 75% of those >64 y with vitamin B_{12} deficiency do not have anemia or even RBC abnormality. CDC states that 1 in 31 individuals 51 y of age or older are deficient in B_{12}.
- Prescribed for pernicious anemia and demyelinating CNS disease.
- Lack of gastric secretion of intrinsic factor leads to malabsorption of vitamin B_{12}; therefore IM route preferred. Recent studies have documented that high-dose oral replacement is effective. Strict vegetarian diet–induced deficiency state responds to oral supplementation.
- Until a person reaches midlife, he or she probably gets all the B_{12} needed from food (unless vegetarian). Autoimmune achlorhydric gastritis (pernicious anemia) decreases absorption because of loss of intrinsic factor. Pts are also almost certainly low on B_{12} if they have been taking a proton pump inhibitor for a long time, which seriously diminishes B_{12} absorption. B_{12} absorption also generally decreases with older age.
- Also associated with *Helicobacter pylori* infection, chronic alcohol ingestion, long-term metformin administration, and pancreatic exocrine deficiency conditions.

Worry About

- Permanent neurologic injury, classic combined system disease with paresthesias, balance problems with loss of position and vibratory sense, and lack of myelination in long tracts; preventable with recognition and cobalamin replacement.
- Interactions and neurologic injury with folate, methionine synthetase inhibitors, and nitrous oxide, which can produce rapid neurologic deterioration.
- Hyperhomocysteinemia, which causes thrombophilia and vascular disease, associated with adequate folate and B_{12} deficiency.

Overview/Pharmacology

- Vitamin B_{12} released from dietary proteins by acid and peptic action binds to intrinsic factor (gastric glycoprotein from parietal cells) in the GI tract, is absorbed from the ileum, bound to transcobalamin II in plasma for transport to tissues. Approximately 3 μg of cobalamin secreted into bile daily.
- Excess vitamin B_{12} administration increases urinary excretion.
- Vitamin B_{12} is enzymatically converted to two active forms: deoxyadenosylcobalamin and methyl-cobalamin.

- Deoxyadenosylcobalamin is a cofactor for mitochondrial mutase enzyme, which catalyzes L-methylmalonyl CoA to succinyl CoA.
- Methylcobalamin is a cofactor in methionine synthetase reaction (a methyl group is transferred from 5-methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate); pivotal in normal synthesis of purines, pyrimidines, and a number of methylation reactions through formation of *N*-adenosylmethionine.

Drug Class/Mechanism of Action/ Usual Dose

- Water-soluble B-vitamin complex.
- Administered via the IM or deep SQ route in doses of 1–1000 μg.
- Oral dose of 1000–2000 μg is as effective as IM dosing in pernicious anemia.
- Needs glycoprotein (intrinsic factor 60,000 MW) produced by gastric parietal cells for its absorption; 0.5–4% absorbed by passive diffusion without intrinsic factor.
- RDA: 2.4 μg/d for adults.
- Vitamin B_{12} is a quiet, conscientious type: doesn't get much hype, yet works overtime to keep your brain, immune system, and ticker in good shape; may protect against Alzheimer disease, depression, stroke, and vision loss.
- Therapeutic 1000 μg IM every mo or 1000 μg orally per d.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
GI	Achlorhydric or gastrectomy pts at risk; associated with atrophic glossitis	Burning and tingling of mouth	Small, slick, glistening tongue	Serum B_{12} decreased, homocysteine and methylmalonic acid increased
HEME	Megaloblastic anemia	Apathy, lassitude, fatigue	Pale skin and mucous membranes, especially nailbeds, palmar surfaces	Peripheral blood smear: Macrocytic hyperchromic RBCs Bone marrow: Megaloblasts, megakaryocytes Plt count
CNS	Degeneration of dorsal, lateral columns of spinal cord	Numbness, tingling in extremities, difficulty walking	Loss of vibration, vibration, position sense; ataxia, Romberg sign, muscle flaccidity	Serum B_{12} <200 pg/mL, serum methylmalonic acid >400 nmol/L, and serum homocysteine >21 μmol/L suggests B_{12} deficiency
PNS	Neuropathy	Paresthesias, dysesthesias of lower extremities		

Key References: Hillman RS: Hematopoietic agents: growth factors, minerals, and vitamins. In Hardman JG, Limbird LE, editors: *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 9, New York, 1996, McGraw-Hill, pp 1311–1340; Stabler SP: Vitamin B_{12} deficiency, *N Engl J Med* 368(2):149–160, 2013.

Perioperative Implications/Possible Drug Interactions

- Folate administration reverses megaloblastic anemia but does not prevent (may precipitate) spinal cord degeneration.
- N_2O oxidizes vitamin B_{12}, reduces the activity of methionine synthetase.
- Effect of N_2O can be reversed by large doses of folic acid.

Anticipated Problems/Concerns

- Scavenging of waste anesthetic gas prevents OR personnel from developing vitamin B_{12} deficiency states due to prolonged exposure to N_2O.
- Extensive interaction between folate and vitamin B_{12} makes it imperative that pernicious anemia be treated with B_{12} at same time as folate to prevent CNS degeneration.

Warfarin (Coumadin)

Charise T. Petrovitch | Lee A. Fleisher

Uses

- Management of thromboembolic disorders: For prophylaxis, Rx, and prevention of recurrence of thromboembolic events including DVT, pulm embolism, thrombosis of grafts. Prevention of arterial emboli associated with prosthetic heart valves, nonvalvular AFib, acute MI. Prevention of MI, stroke, and recurrent MI. Rx for deficiency of antithrombin III, protein C, protein S.
- Unknown number of individuals receiving the drug.

Perioperative Risks

- Hemorrhage (minor to major life risk)
- Purple-toe syndrome or warfarin necrosis
- Teratogenicity in pregnancy (decreases synthesis of vitamin K-dependent clotting factors by fetus)
- Risk of thrombosis/bleeding if discontinued periop

Worry About

- Major drug interactions
- Many drugs affect action of warfarin. List is extensive and continually expanding. Be concerned about other drugs that potentiate bleeding (e.g., antiplatelet agents, ASA, NSAIDs); and drugs that displace warfarin from protein-binding sites or that increase or decrease vitamin K levels.

Overview/Pharmacology

- General effect: Anticoagulant with dose-dependent effect on coagulation

Pharmacokinetics/Pharmacodynamics

- Warfarin is a racemic mixture of R and S isomers (R-warfarin and S-warfarin).
- Racemic warfarin is absorbed rapidly from GI tract; reaches maximal plasma concentration in 90 min; has a half-life of 36–42 h; time to peak effect is 36–72 h; duration after discontinuation is at least 2–5 d.
- In circulation, bound to plasma proteins and accumulates in liver. R-warfarins are excreted in urine; S-warfarins are eliminated in bile.
- Warfarin resistance or decreased warfarin effect. When warfarin absorption from GI tract is impaired due to malabsorption syndromes, concurrent use of liquid paraffin laxatives, cholestyramine resin, or excessive amounts of certain antacids (e.g., Mg trisilicate).
  - Vitamin K intake increased through diet or administration of vitamin K IM or IV.
  - With induction of hepatic enzymes, increasing metabolism of warfarin. Enzyme inducers including anticonvulsants, barbiturates, primidone, carbamazepine, antimicrobials (e.g., griseofulvin, rifampin, nafcillin, ethanol) and smoking.
- Increased warfarin effect or warfarin sensitivity
  - Drugs displacing warfarin from albumin increase its bioavailability (NSAIDs, ASA, phenytoin sodium, oral hypoglycemic agents, sulfa drugs, nalidixic acid, estrogen, miconazole)
  - Deficiency of vitamin K enhances; occurs with malabsorption syndromes and during administration of liquid paraffin laxatives and clofibrate; after long-term use of oral antimicrobials that deplete intestinal bacterial source of vitamin K. Large doses of vitamin E antagonize the action of vitamin K; anabolic steroids, danazol impair synthesis of vitamin K-dependent clotting factors; olestra removes vitamin K.
  - Metabolism blocked by phenytoin, chloramphenicol, erythromycin, clofibrate, TCAs, cimetidine, sulfinpyrazone, and trimethoprim-sulfamethoxazole, thus increasing warfarin's effect. Disulfiram (Antabuse) significantly slows metabolism.
  - Certain cephalosporins have a warfarin effect themselves—thus they are contraindicated.
  - Elderly, febrile, and debilitated pts and those with hepatic dysfunction, hyperthyroidism, or heart failure may have increased warfarin effect.

Drug Class/Mechanism of Action/ Usual Dose

- Interferes with synthesis of 6 vitamin K–dependent proteins involved in coagulation sequence: Factors II, VII, IX, and X; proteins C and S. Before these proteins are released into circulation, they undergo reactions that convert glutamic acid residues to carboxyglutamic acid residues and require presence of reduced form of vitamin K.
- Inhibits cyclic interconversion between reduced form of vitamin K and its 2,3-epoxide (vitamin K epoxide).