- 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).

- Defective clotting factors lacking a "carboxyl tail" are produced, impairing coagulation.
- Factor II has a half-life of 48 h; requires 3–4 d to drop to a level when PT significantly prolonged.
- Nonurgent need for anticoagulation: Adult with average body mass, 5 mg/d PO prolongs PT to 1.5 × control value in 36–48 h; if not achieved by third day, daily dose may be adjusted by an increase or decrease of 2.5 mg; goal: PT = 1.5–2 × control. Increases bleeding complications when PT is 2.5 × control. Once anticoagulation stabilized, warfarin dose should be adjusted to maintain INR of 2–3 for all indications except in the case of mechanical prosthetic cardiac valves, which require higher levels of anticoagulation.
- More urgent need: Heparin anticoagulation first; start warfarin, 10 mg for 2 d.

Assessment Points

System	Effect	Assessment by History	Physical Examination	Test
GI	Vitamin K deficiency may result from a poor diet, extrahepatic biliary obstruction, malabsorption, sterile gut	GI bleeding Tarry stools Hematemesis	Weight/height ratio (BMI)	Hct Fecal occult blood
ENDO	Vitamin K deficiency Hyperthyroidism, hypermetabolism potentiate warfarin effect		Malnourishment	PT/PTT INR
GU	Diuresis, pregnancy decreases effect; warfarin is teratogenic			PT/PTT INR
MS	Arthritis pain medications that affect platelets (e.g., ASA, NSAIDs) potentiate bleeding			

Key References: Douketis JD, Spyropoulos AC, Kaatz S, et al.: BRIDGE investigators: perioperative bridging anticoagulation in patients with atrial fibrillation, *N Engl J Med* 373(9):823–833, 2015; van Veen JJ, Makris M: Management of peri-operative anti-thrombotic therapy, *Anaesthesia* 70(Suppl 1):58–67, 2015.

Perioperative Implications

Preoperative Concerns

- Anticoagulation: Consider therapy with vitamin K (PO, IM, IV, SQ: 2.5–5 mg/70 kg) or FFP (15–20 mL/kg).
- Monitor this drug: PT, INR.
- Decision to continue warfarin in pt undergoing surgery depends on risk of thrombosis vs risk of bleeding. In pts with atrial fibrillation in the BRIDGE trial, forgoing bridging anticoagulation was noninferior to periop bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding.

Possible Drug Interactions

- Regional: Risk of spinal or epidural hematoma when performing a regional when pt is anticoagulated. Risk is theoretically increased with anticoagulant. Epidural cath thought to be associated with greater risk of spinal or epidural hematoma if no measurable anticoagulant effect from warfarin (e.g., PT normal), but if receiving warfarin, not known if risks of spinal or epidural hematoma are significant.

Anticipated Problems/Concerns

- Bleeding the most likely complication due to further depletion of clotting factors during surgery; factor depletion may follow massive transfusions or with development of DIC.
- If anticoagulation is reversed preop with large doses of vitamin K, warfarin resistance is possible initially; thrombosis a risk in this setting.
- If anticoagulation reversed with administration of FFP, anticoagulation is more easily achieved postop, but infectious risks are a concern.
- Preop dose of warfarin can be restarted with oral fluids; when risk of thromboembolism is considered to be especially high (as in pts with recurrent pulm emboli undergoing pelvic surgery) or a delay of more than 48 h is anticipated before warfarin can be restarted, postop heparin infusion is appropriate.