- Hypotensive effect is primarily through sympathetic blockade by lowering SVR.
- Hypotensive effect is also mediated through direct vasodilation and histamine release (especially at higher rates of administration).
- Usual adult dosage:
  - For controlled hypotension during surgery: Initial: IV infusion, 3–4 mg/min, adjusted according to response; maintenance: IV infusion, 0.3–6 mg/min.
  - For hypertensive emergency: Initial: IV infusion, 0.5–1 mg per min, adjusted according to response; maintenance: IV infusion, 1–5 mg/min.
- Pts on concomitant antihypertensive medications require lower doses.

Assessment Points

System	Effect	Assessment by Hx	PE
HEENT	Mydriasis with cycloplegia	Visual changes	
CV	Vasodilation, tachycardia, hypotension, lowered SVR	Angina, syncope	Orthostatic hypotension
RESP	Rare respiratory arrest (uncertain etiology)		
GI	Decreased secretions, lower tone/motility	Dry mouth Paralytic ileus, constipation, N/V, diarrhea, reflux	
GU	Bladder atony Lower potency	Oliguria or anuria, incomplete emptying Erectile and ejaculation dysfunction	UO
CNS	Less increase in ICP compared with other vasodilators secondary to preserved cerebral autoregulation		
OB	Crosses placenta, may lower fetal GI motility, causing meconium or paralytic ileus		

Key References: Taylor P: Agents acting at the neuromuscular junction and autonomic ganglia. In Hardman JG, Limbird LE editors: *Goodman and Gillman's the pharmacological basis of therapeutics*, 10th ed. New York, 2001, McGraw-Hill, pp 210–211; Trivedi HK, Patel D, Weir MR: Hypertensive urgencies and emergencies. In Singh AK, Agarwal R, editors: *Core concepts in hypertension in kidney disease*. New York, 2016, Springer, pp 203-218.

Perioperative Implications

Preoperative Concerns

- Assess Hx of CAD; check baseline ECG.
- Assess volume status.
- Consider arterial line if trimethaphan infusion is anticipated.

Induction/Maintenance

- May prolong block from succinylcholine or nondepolarizing neuromuscular blockers.
- For controlled hypotension during surgery, it is recommended that infusion be stopped prior to wound closure.
- Monitor ECG for signs of ischemia due to decreased cardiac perfusion from hypotensive state.

Postoperative Period

- Mydriasis from drug may interfere with neurologic checks of postop neurosurgery pts.
- Risk for paralytic ileus is increased when drug infusion is continued for longer than 48 h.
- Pts continued on trimethaphan infusions postop should be monitored in the ICU
- Oral antihypertensive agents should be instituted and thimethaphan discontinued as soon as pt can take oral medication and BP has stabilized.

Anticipated Problems/Concerns

- Not ideal for prolonged infusions because tachyphylaxis can develop within first 48 h of therapy, although this may be attenuated by concomitant use of a diuretic.

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Valproate

Diana Ayubcha | Taras Grosh

Uses

- Most widely prescribed antiepileptic drug worldwide.
- Used in treatment of epilepsy, acute mania, bipolar disease, impulse-control disorders, migraine headaches, and neuropathic pain.

Perioperative Risks

- Hemorrhage
- Platelet dysfunction
- Coagulopathy
- Hyperammonemic encephalopathy
- Seizures with subtherapeutic plasma concentration

Worry About

- Decreased factor VII levels, plt count and function, factor VIII, protein C, fibrinogen, factor XIII, increased lipoprotein (a) levels, acquired von Willenbrand disease.
- Serum valproate levels of >140 µg/mL may be related to low plt levels.
- Children with a trough level of >450 µmol/L or a daily dose of >40 mg/kg are more likely to develop thrombocytopenia.
- Nausea, gastric irritation, diarrhea, hyperammonemia, thrombocytopenia.
- Highly protein-bound (88–92%); may displace other protein-bound drugs and increase their plasma concentration (e.g., warfarin).

Overview/Pharmacology

- Inhibits CYP2C9, glucuronyl transferase, and epoxide hydrolase.
- Undergoes hepatic metabolism (glucuronide conjugation and oxidation) and renal excretion.
- 88–92% protein-bound and can be displaced by competing drugs, thereby increasing the plasma concentration of pharmacologically active drug.
- IV and PO doses are equivalent.
- Inhibits drug-metabolizing enzymes rather than inducing them, like other AEDs.
- Inhibits metabolism of lamotrigine and phenobarbital.
- Plasma concentration decreases with carbapenems.
- May increase the plasma concentrations of a variety of drugs, including zidovudine, lorazepam, nimodipine, paroxetine, amitriptyline, nortriptyline, nitrosoureas, and etoposide.

Drug Class/Mechanism of Action/ Usual Dose

- Antiepileptic
- Delays reactivation of Na+ channels during high-frequency neuronal firing, producing an inhibitory effect on creation of action potentials until neuronal discharge is blocked; works at both Na+ and Ca+ channels.
- Increases synthesis and release of GABA reduces GHB, and inhibits NMDA
- Usual dose: 500–3000 mg/d in 2–4 divided doses.
- Therapeutic trough 50–100 µg/mL.

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.