- TXA was associated with reductions in mortality of 5–54% in pts with upper GI bleeding compared with placebo. Meta-analysis indicated a reduction of 40%.
- Administered either PO at 25 mg/kg every 6–8 h or IV at 10 mg/kg every 6–8 h beginning on the d prior to surgery.
- In adults, the minimum concentration of TXA necessary to completely prevent fibrinolysis is 17.5 ug/mL.
- In children aged 2 d-4 y, body weight is less accurate at predicting the distribution and elimination of TXA. Dosing is recommended by age rather than body weight. Other factors that do not affect the distribution and elimination of TXA in children are body surface area, pump prime volume, ultrafiltrate volume, and body temperature.
- Neonatal plasma requires a significantly lower concentration of TXA than adult plasma.
- In neonates the minimum concentration of TXA to completely prevent fibrinolysis is 6.54 µg/mL.
- Absorption after oral use is 30–50%; bioavailability is not affected by food.
- An antifibrinolytic concentration of drug remains in serum up to 7–8 h.
- The protein binding to plasminogen is approximately 3% at therapeutic plasma levels; it does not bind to serum albumin.
- The half-time of elimination when administered orally is 120 min.
- Urinary excretion is the main route of elimination via glomerular filtration.
- Overall renal clearance is equal to overall plasma clearance, and >90% of the dose is excreted unchanged in 24 h.
- Pts with renal insufficiency should have their doses reduced according to creatinine clearance. Only a small fraction of TXA is metabolized.
- TXA is 6–10 times more potent in terms of binding to plasminogen/plasmin than ε-ACA.
- Concurrent administration of heparin does not influence the activity of TXA.
- Pharmacokinetic properties: Maximum plasma concentrations of TXA can be attained within 3 h after an oral dose. Elimination after IV administration is triexponential, and over 95% of each dose is eliminated unchanged in the urine.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Retinal degeneration is associated with prolonged use; incidence 25–100% and dose-dependent (animal studies)	Visual changes	Ophthalmologic exam in pts receiving TXA every 4–5 d	Visual acuity Visual field Color vision Eyeground
CV	Hypotension (with rapid infusion)	Mental status changes, nausea	BP monitoring, HR, ECG	
RENAL	Reduce dose in pts with renal insufficiency			BUN/Cr, CrCl
GI	N/V, diarrhea, abdominal discomfort			
OB	Category B No well-controlled studies in pregnant females	Crosses placenta and appears in cord blood at concentration equal to that in maternal blood		
IMMUNE	Male mice receiving TXA up to 5 g/kg per d have been found to develop leukemia			

Key References: Fergusson DA, Hérbert PC, Mazer CD, et al.: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery, *N Engl J Med* 358(22):2319–2331, 2015; Kagoma YK, Crowther MA, Douketis J, et al.: Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials, *Thromb Res* 123(5):687–696, 2009.

Perioperative Implications

Airway
- No interactions known

Preinduction/Induction
- If given IV, inject slowly to avoid hypotension.

Maintenance
- No interactions known

Emergence
- No interactions known

Adjuvant/Regional Anesthesia/Reversal
- No interactions known

Contraindications
- Acquired defective color vision: Prohibits measuring one endpoint of toxicity.
- Subarachnoid hemorrhage: Cerebral edema and cerebral infarction may be caused by TXA in pts with subarachnoid hemorrhage.

Active Thromboembolic Disease
- Caution in the setting of DIC, in which inhibition of fibrinolysis may aggravate the hypercoagulable state.
- Reduced dose in renal insufficiency.

Anticipated Problems/Concerns

- Potential for increased thrombotic events.
- Timing of administration appears to be critical for optimal effect of hemostasis without increasing risk of thromboembolism.
- Single-dose administration of TXA is not effective in treating maximum reduction of blood loss.

Trimethaphan

Stephen T. Robinson

Uses

- Production of controlled hypotension during surgery to reduce bleeding into the surgical field
- Rapid reduction of BP in the treatment of hypertensive emergencies
  - Treatment of acute dissecting aortic aneurysm, particularly when preexisting conditions make the use of beta=blockers a relative contraindication
  - Emergency treatment of pulm edema in pts with pulm Htn associated with systemic Htn
- May serve as an alternative to sodium nitroprusside for pts who are resistant to this drug or can be mixed with nitroprusside to decrease risk of cyanide toxicity from nitroprusside

Perioperative Risks

- High doses may cause profound hypotension and, rarely, respiratory arrest.
- QRS prolongation has been seen during treatment.
- Tachycardia, angina, or syncope may occur without warning.
- Because of trimethaphan's ability to cross the placenta, its ganglionic blocking effects may decrease GI motility in the fetus, resulting in meconium ileus or neonatal paralytic ileus.
- CNS examination is limited by production of mydriasis.

Worry About

- Contraindicated in pts with shock, anemia, hypovolemia, uncorrected respiratory insufficiency, or neonates at risk for paralytic or meconium ileus.
- Orthostatic hypotension; may cause severe hypotension.
- Difficult to obtain since it is no longer manufactured in USA.

Overview/Pharmacology

- Rapid-acting ganglionic acetylcholine blocker, onset within 1–3 min.
- Peak response within 5–10 min.
- Duration of action: 10–15 min for single dose.
- Affects both parasympathetic and sympathetic pathways.
- Renally excreted, mostly unchanged.
- Most side effects are due to parasympathetic blockade and respond to dose reduction or discontinuation.
- Cardiac output may increase in pts with CHF or decrease in pts with normal heart function.
- Tachyphylaxis may occur during continuous IV infusion.

Drug Class/Mechanism of Action/ Usual Dose

- A short-acting ganglionic blocking agent.
- Prevents stimulation of postsynaptic receptors by competing with acetylcholine for these receptor sites.

- 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.