- Plasminogen activator inhibitors, also released by endothelial cells, oppose the action of t-PA and may be a factor in preventing uncontrolled fibrinolysis.

Drug Class/Mechanism of Action/ Usual Dose

- Thrombolytic agent. Binds to fibrin threads of thrombus and converts enmeshed plasminogen to plasmin, which initiates localized fibrinolysis. For this reason, unlike streptokinase, t-PA can be considered fibrin-specific; t-PA lacks effect on circulating plasminogen, thereby limiting systemic effects.
- For STEMI:
  - Accelerated infusion (<67kg) dose: 15mg IV once, then 0.75 mg/kg (max 50 mg) over 30 min, then 0.5 mg/kg (max 35 mg) over 60 min.
  - Accelerated infusion (>67 kg) dose: 15 mg IV once, then 50 mg over 30 min, then 35 mg over 60 min; max 100 mg total.
  - 3-h infusion (<65 kg) dose: 1.25 mg/kg IV over 3 h; 60% of dose over 1 h with 6-10% of dose as IV bolus, then 20% over second h, then 20% over third h.
  - 3-h infusion (>65 kg) dose: 100 mg IV over 3 h; 60 mg over 1 h with 6-10% of dose as IV bolus, then 20 mg over second h, then 20 mg over third h; max 100 mg total.
- Amount of salvaged myocardium is directly related to the time until the occluded artery is reopened. GUSTO I investigators showed 84% patency within 6 h of front-loaded t-PA.
- In acute ischemic stroke, 0.9 mg/kg IV with 10% given as loading bolus over 1 min and remainder infused over 60 min. Dose not to exceed 90 mg.
- In pulm embolism, 100 mg IV over 2 h. Start heparin at end of t-PA infusion.
- More rapid lysis, less systemic fibrinolysis, not antigenic and rarely associated with allergic reaction when compared with streptokinases, but t-PA is more expensive.

Assessment Points

System	Effect	Assessment by Hx	PE	Treatment
CV	Bleeding from vascular puncture sites	Hematoma Check for retroperitoneal bleed in presence of femoral puncture	Hgb	Manual compression Rarely is blood transfusion necessary
	Severe bleeding during surgery	Check if heparin or plt IIb/IIIa blockers are being given	Hgb Plts APTT	Transfusion of blood, FFP, cryoprecipitate Factor VIII and Plts may be needed; consider using TEG to guide therapy
	Effects of ancillary treatment	Check for ongoing beta-blocker, nitroglycerin, or morphine treatment		Discontinue if necessary; however, beta blockade has considerable benefit with little risk in most pts
	Reperfusion arrhythmias	Can occur on restoration of blood flow to ischemic myocardium	CV stability	Antiarrhythmics
CNS	Intracranial hemorrhage	Signs of stroke or raised ICP	Neurologic assessment Urgent CT, MRI	Supportive BP control (risk is increased in presence of heparin)

Key References: GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction, *N Engl J Med* 329(10):673–682, 1993; Schellinger PD, Fiebach JB, Mohr A, et al.: Thrombolytic therapy for ischemic stroke—a review. Part I—Intravenous thrombolysis, *Crit Care Med* 29(9):1812–1818, 2001.

Perioperative Implications

- High bleeding risk with invasive line placement
- Risk of hypotension on anesthetic induction with adjuvant nitroglycerin infusion
- Severe Htn may predispose to or exacerbate hemorrhagic stroke
- Residual thrombus is highly thrombogenic, posing risk of rethrombosis
- Contraindication to regional/spinal anesthesia
- Increased need for transfusions
- Close monitoring of neurologic function preop and postop

Tranexamic Acid

Alan David Kaye | Adam M. Kaye | Shilpadevi S. Patil | Debbie A. Chandler | Elyse M. Cornett

Uses

- To prevent bleeding due to fibrinolysis after surgery or trauma (cardiac surgery with and without cardiopulmonary bypass; liver transplantation; orthopedic surgery including spine; GU surgery; peripartum hemorrhage). Bleeding can be diagnosed clinically or via lab tests (prolonged thrombin time, reduced fibrinogen levels, increased D-dimer levels, classic teardrop shape on thromboelastography).
- Antifibrinolytic choice in cardiac surgery has shifted from aprotinin to TXA and epsilon-aminocaproic acid (ε-ACA) owing to the concern that aprotinin may be associated with an increased risk of cardiovascular or cerebrovascular events, renal dysfunction, or renal failure.
- TXA in 6% hydroxyethyl starch 130/0.4 prime solution decreases blood loss and chest tube drainage in CABG with no renal or postop complications.
- The reduction of blood loss in orthopedic surgery is of great importance, especially in hip or knee arthroplasty and spinal surgery. TXA administered at 10–15 mg/kg IV reduces blood loss, reduces relative risk of transfusion, and poses no increased risk of thromboembolism.
- Effective in reducing periop blood loss and transfusion requirements in neonates and children undergoing craniosynostosis reconstruction surgery and repair of congenital heart defects.
- TXA application in trauma is supported by firm clinical evidence. IV loading of 1 g TXA within 8 h of trauma then followed by IV infusion of 1 g TXA over 8 h significantly reduced all-cause mortality and death due to bleeding.
- PPH is a major cause of maternal mortality. TXA is used as a complement to uterotonics and appears to be a promising drug for the prevention and treatment of PPH after both vaginal and cesarean delivery.
- Used to reduce placental bleeding and conization of the cervix.
- For short-term use (2–8 d) in pts with hemophilia or von Willebrand disease to reduce or prevent hemorrhage and to reduce the need for replacement therapy during and following tooth extraction.
- To treat primary menorrhagia, gastric and intestinal hemorrhage, urinary tract bleeding, recurrent epistaxis, and hereditary angioneurotic edema. The drug also inhibits induced hyperfibrinolysis during thrombolytic treatment with plasminogen activators.
- Used in pts with hemophilia or those receiving anticoagulation who are about to undergo oral surgery.

Perioperative Risks

- Side effects: N/V, diarrhea, and abdominal pain are the most common adverse effects (in approximately 30% of pts with oral use).
- Giddiness has been reported.
- Hypotension (if the drug is injected too rapidly).

Worry About

- Potential for thrombotic complications secondary to the inhibition of fibrinolysis

Overview/Drug Class

- A synthetic lysine analogue. Prevents plasmin formation and therefore fibrinolysis by occupying plasminogen's lysine-binding site for fibrin.
- Has a structure similar to that of lysine and reversibly binds to lysine-binding sites for fibrin on plasminogen, thereby blocking the binding of plasminogen to fibrin. Plasminogen activators are located on the fibrin clot. Without localized binding of plasminogen to fibrin, it cannot be converted to plasmin.
- Because fibrinolysis requires plasminogen (and plasmin) binding to fibrin, fibrinolysis is inhibited.
- A competitive inhibitor of plasminogen activation and, at much higher concentrations, a noncompetitive inhibitor of plasmin. Suppresses fibrinolysis by inhibiting activation of plasminogen.
- Other antifibrinolytic medications incl ε-ACA (lysine analogue) and aprotinin (serine protease inhibitor).
- Reductions in mortality rates with TXA doses of 4.5–6 g daily for 5–7 d (in most studies) produced statistical significance between TXA and placebo.

- 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.