# Thyroid Supplements

John M. Murkin

## Uses

- More than 3 million chronic users in USA.
- $T_4$ prescribed for pts with chronic hypothyroidism.
- $T_3$ used in myxedema coma.
- $T_3$ successfully used as rescue therapy for cardiogenic shock after CPB.
- $T_3$ favorably administered to brain-dead donors before organ harvesting for heart or heart-lung transplantation. (Prophylactic use of $T_3$ has shown no benefit in recent randomized trials.)
- $T_4$ is generally administered PO; $T_4$ and $T_3$ can be administered IV.

## Perioperative Risks

- Drugs (amiodarone, lithium, herbal supplements, catecholamines, radiopaque contrast media) and also cirrhosis, renal failure, sepsis, and operation (CPB) can induce euthyroid sick syndrome (reduced peripheral conversion of $T_4$ to $T_3$); may also precipitate myxedema coma.
- Amiodarone, a potent class III antiarrhythmic drug, is an iodine-rich compound with a structural resemblance to $T_3$ and $T_4$ and causes substantial iodine overload; with continued administration, may produce either thyrotoxicosis or hypothyroidism.

## Worry About

- $T_4$ or $T_3$ can aggravate symptoms of myocardial ischemia.

## Overview/Pharmacology

- Hypothyroidism (overt) estimated to affect 0.5–3.8% of adults and increases with age (over 15% of women at ≥age 60).
- After thyroidectomy, <30% of pts euthyroid at 10 y due to inadequacy or discontinuation of Rx.
- Reversal of clinical Sx of chronic hypothyroidism, including myocardial effusions, requires 2–4 mo Rx.
- Half-life of $T_4$ is 7 d; $T_3$ is 1.5 d.
- $T_4$ is a relatively inactive prohormone that undergoes monodeiodination in liver and kidney to biologically active $T_3$.

## Drug Class/Mechanism of Action/ Usual Dose

- Thyroid hormone replacement Rx.
- $T_3$ binding to specific membrane receptor proteins augments membrane transport activity, mitochondrial oxidative phosphorylation, and protein synthesis.
- Extranuclear effects of $T_3$ occur within min, increasing myocardial mitochondrial and transmembrane transport activity.
- Nuclear effects of $T_3$ occur within 0.5–1 h, involving transcription and translation of myocardial enzymes and contractile proteins.
- Direct effect of $T_3$ decreases arterial smooth muscle tone.
- Usual dosage of $T_4$ is 0.15 mg/d PO.
- Acute Rx: $T_4$, 0.3–0.5 mg by slow IV infusion followed by 0.1–0.15 mg/d, or $T_3$, 0.005–0.01 mg IV.

## Assessment Points

| System | Effect | Assessment by Hx | PE | Test |
|---|---|---|---|---|
| CV | Chronotropy, inotropy, reduced SVR<br>Arrhythmogenesis | Less fatigue<br>Palpitations | HR, reflexes | $FT_4E$, TSH, ECG |
| RESP | Restoration of hypoxic, hypercapnic ventilatory drive | | | |
| GI | Increased protein synthesis; enhanced hepatic, renal clearance/excretion functions | | Normal skin turgor | |
| ENDO | Thermogenesis | Reversal of cold intolerance | Skin warm to touch | |

**Key Reference:** Kohl BA, Schwartz S: Surgery in the patient with endocrine dysfunction, *Anesthesiol Clin* 27(4):687–703, 2009.

## Perioperative Implications/Possible Drug Interactions

### Preoperative Concerns

- Thyroid hormones increase breakdown of vitamin K–dependent clotting factors, which can alter coagulation status.
- Chronic amiodarone therapy may produce hyper- or hypothyroidism and has been specifically associated with thyrotoxicosis.
- Preop low free $T_3$ syndrome ($FT_3$ <2.23 pmol/L) has been associated with an increased risk of low cardiac output and death in coronary revascularization pts.

### Induction/Maintenance

- $T_4$ administration is advocated in the management of organ donors; oral $T_4$ achieves approximately 91–93% of the bioavailability of IV thyroxine and also facilitates hemodynamic stability comparable with IV administration.
- Exaggerated Htn and tachycardia can occur with agents such as ketamine and exogenous catecholamines including ephedrine and epinephrine in pts on both acute and chronic thyroid hormone replacement.

### Adjuvants/Regional Anesthesia/Reversal

- Anticholinergics with minimal CV effects (e.g., glycopyrrolate) preferred over atropine.
- Caution in the presence of spinal anesthesia; $T_3$ administration may produce aggravated hypotension.

### Postoperative Period

- Cirrhosis, sepsis, renal failure, surgery may all decrease peripheral conversion of $T_4$ to $T_3$ (euthyroid sick syndrome) and precipitate hypothyroidism.

## Anticipated Problems/Concerns

- In critically ill pts, $T_3$ replacement can produce detrimental increases in oxygen requirements (especially myocardial) and protein catabolism without improving mortality rates.

# Tissue Plasminogen Activator

Alan David Kaye | Burton D. Beakley | Ken F. Mancuso

## Uses

- Clinical indications for thrombolysis in treatment of pulmonary embolism, acute ischemic stroke, acute MI, and occluded central venous access devices.
  - MI: Administration as soon as possible from symptom onset
  - Stroke: Administration within 3 h from onset of symptoms
- Rapid clot lysis by t-PA offers advantages in comparison with streptokinase.
- May be used in combination with other anticoagulants such as heparin and aspirin. Also may be combined with beta-blockers, morphine, nitroglycerin, and plt IIb/IIIa blockers.

## Perioperative Risks

- Increased risk of bleeding during surgery; if severe, possible need for blood transfusion, fresh frozen plasma, cryoprecipitate, and plt infusion therapy.
- Strict blood pressure monitoring with intraop Htn posing increased risk of intracranial hemorrhage (0.8% with acute MI therapy and 6% with acute ischemic stroke therapy).
- Incomplete restoration of coronary blood flow and persisting thrombogenicity may lead to cardiac instability and risk for periop infarction.

## Worry About

- Severe hemorrhagic complications and intracranial hemorrhage.
- Invasive procedures: Damage to blood vessels during vascular access procedures can cause severe bleeding, especially at noncompressible sites (e.g., subclavian vein).
- Risk for hematoma formation causing damage via mass effect to surrounding tissue/vessels (e.g., ulnar nerve during arterial cannulation).
- Contraindication for spinal/regional anesthesia.
- Bleeding at venipuncture sites.

## Overview/Pharmacology

- Thrombolytic agent: Natural t-PA is produced by vascular endothelial cells and is naturally released from the endothelium in response to venous occlusion, physical activity, stress, or vasoactive medications. Responsible for most of the body's effort to prevent excessive thrombosis.
- Accelerates the conversion of plasminogen (bound to fibrin) to plasmin, resulting in fibrinolysis as site of clot.
- Time-dependent, because older thrombi develop extensive fibrin polymerization, making them more resistant to thrombolysis.
- t-PA (alteplase) is commercially produced using cDNA for natural t-PA, which is then is transfected into a mammalian cell line.
- Initial thrombolytic response is seen within 30 min when given IV. Half-life is about 5 min; elimination half-time is about 30–50 min. Some 80% is cleared from plasma within 10 min of stopping a standard infusion, and clearance is via the liver.

- 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<br>Check for retroperitoneal bleed in presence of femoral puncture | Hgb | Manual compression<br>Rarely is blood transfusion necessary |
| | Severe bleeding during surgery | Check if heparin or plt IIb/IIIa blockers are being given | Hgb<br>Plts<br>APTT | Transfusion of blood, FFP, cryoprecipitate<br>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<br>Urgent CT, MRI | Supportive<br>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

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### 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.