Tissue Plasminogen Activator (t-PA)–Alteplase

Brand names	Activase, Cathflo Activase
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names ISMP reports that Activase has been confused with TNKase.[2] USP reports that alteplase has been confused with TNKase. Activase has been confused with Retavase and TNKase.[3]
Contraindications and warnings	**Contraindications**[4] **In patients with acute myocardial infarction or pulmonary embolism, the following are contraindications:** Active internal bleeding; history of recent stroke; recent (within 3 months) intracranial or intraspinal surgery or serious head trauma; intracranial neoplasm associated with increased bleeding risk, arteriovenous malformation or aneurysm; bleeding diathesis; or current severe uncontrolled hypertension. **In patients with acute ischemic stroke, the following are contraindications:** Intracranial hemorrhage; subarachnoid hemorrhage; intracranial or intraspinal surgery or serious head trauma in the past 3 months; current severe uncontrolled hypertension; active internal bleeding; intracranial neoplasm associated with increased bleeding risk, arteriovenous malformation or aneurysm; or bleeding diathesis. In patients without recent oral anticoagulant or heparin use, discontinue t-PA infusion if pretreatment international normalized ratio (INR) >1.7 or activated partial thromboplastin time (aPTT) is elevated. **Warnings:** Bleeding is the most common complication.[4] Before thrombolytic therapy is used, clinicians should correct other concurrent hemostatic problems, such as thrombocytopenia or vitamin K deficiency.[5]
Infusion-related cautions	Extravasation can cause ecchymosis and inflammation.[4] The infusion should be stopped and local treatment applied.
Dosage	**Recommendations for use of thrombolytics in pediatrics**[5] **Neonates with a major vessel occluded and perfusion of limbs or vital organs that are being compromised:** If thrombolytics are needed, plasminogen (fresh frozen plasma) should be given prior to infusion. **Children with venous thromboembolism:** Thrombolysis is recommended only for life- or limb-threatening thrombosis. If it is used and plasminogen deficiency is present, plasminogen should be supplemented. **Bilateral renal vein thrombosis with renal impairment:** Options include initial anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), or t-PA followed by UFH/LMWH. **Neonates with blocked central venous access devices (CVADs):** Local thrombolysis after appropriate clinical assessment **Infants and children with blocked CVADs:** Thrombolytic should be used to restore patency. A second dose may be instilled if the catheter remains blocked after the first instillation. **Children with limb-threatening or organ-threatening femoral artery thrombosis who fail initial UFH therapy:** Thrombolysis **Neonates and children with symptomatic peripheral artery catheter-related thromboembolism:** Unfractionated heparin with or without thrombolysis or surgical thrombectomy

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Dosage *(cont.)*

Systemic thrombolytic therapy: 0.1–0.6 mg/kg over 10–20 minutes (if a bolus is desired)[6-8] followed by infusion of 0.02–0.6 mg/kg/hr.[6,9-20] Because of bleeding tendencies in 50% of patients, some suggest that initial doses of 0.1 mg/kg/hr be increased gradually up to 0.5 mg/kg/hr if clot dissolution does not occur at lower doses.[10,11,21] Another suggests 0.5 mg/kg/hr for 1 hour followed by 0.25 mg/kg/hr for 4–11 hours until clot lysis occurs; however, the incidence of bleeding was still approximately 50% with the lower infusion rate.[19] Two studies reported that continuous infusion for 8–11 days in neonates did not result in resolution of the thrombus and was associated with bleeding.[22,23] In 27 newborns at risk of organ or extremity loss due to a thrombus that had failed to respond to UFH, t-PA was given at 0.1–0.6 mg/kg/hr × 6 hours for up to 6 days (no loading dose). Median 2 doses given; 47% had complications, most commonly, bleeding.[60] A 2-year-old with a superior vena cava thrombus was treated successfully through a peripheral vein with 0.03 mg/kg/hr for 48 hours in combination with LMWH.[25] A 22-month-old with superior vena cava thrombosis received 1.5 mg/kg IV over 2 hours once daily for 2 days, after failing initial therapy with UFH.[26]

Local or catheter-directed thrombolysis: Dosing not established; all data from case reports or small studies. Three infants with brachial artery thrombosis and significant hand ischemia received UFH and intra-arterial t-PA (0.05 mg/kg).[27] Local instillation of low-dose (0.01–0.06 mg/kg/hr) was effective in 12 of 17 children with acute thrombosis.[28]

Acute ischemic stroke: Dosing not established in pediatrics, however, a multinational expert consensus treatment protocol was designed (the Thrombolysis in Pediatric Stroke [TIPS] trial, which was stopped early due to low recruitment but authors suggest that the regimen may offer guidance to clinicians). t-PA regimens in this trial were 0.75 mg/kg, 0.9 mg/kg, and 1 mg/kg (maximum doses to be reached at 90 kg weight); 10% of dose to be infused in the first 5 minutes with remainder over next 55 minutes. Dose to be instituted within 4.5 hours of stroke onset. Study protocol has selective inclusion criteria and extensive exclusion criteria.[61] Additional dosing from case reports: 2.5 mg (0.11 mg/kg) given in repeated small boluses intra-arterially for middle cerebral artery occlusion.[24] Two case reports describe t-PA for stroke in fully anticoagulated patients: a 29-month-old child with a ventricular assist device on enoxaparin (anti-Factor Xa 1 unit/mL), aspirin and dipyridamole received catheter-directed intra-arterial t-PA 0.1 mg/kg into an internal carotid artery thrombus followed by 0.1 mg/kg/hr × 24 hours[62]; a 10-month-old baby on enoxaparin and aspirin with embolic stroke of middle cerebral artery received 0.9 mg/kg t-PA (10% in first minute followed by remainder over 60 minutes).[63] Both patients regained neurologic function (not completely back to baseline); neither suffered adverse events from t-PA.

Catheter occlusion

CVAD occlusion: Current manufacturer recommendations: (patients ≥30 kg) 2 mg in 2 mL; (patients <30 kg) 110% of internal lumen volume of catheter, not to exceed 2 mg/2 mL.[29] If patency is not restored after 120 minutes, a second dose may be administered.[29] Many dosing regimens have been reported in the literature. Depending on catheter volume, 0.5–2 mg (solution of 1 mg/mL) for a dwell time of 20 minutes to 4 hours.[30-39] Some catheters may require more than one instillation.[30,31,33,35-37,39] One center reported equal efficacy and safety (from a retrospective review) with t-PA infusion into partially occluded catheters using 0.1 mg/kg (maximum 2 mg) in 25 mL NS over 3 hours compared to standard manufacturer-recommended dwell.[64]

Hemodialysis catheters: Manufacturer recommendations as above for CVAD occlusion. Additional data from small studies or case reports describe efficacy with t-PA infusions (if partial occlusion): 0.1 mg/kg (maximum 2 mg) in 25 mL NS over 3 hours (infants/children)[64]; 2.5 mg in 25 mL NS (children)[40] or in 50 mL NS (*adults*)[41] over 2–3 hours. In all studies, t-PA successfully restored patency in 90–91% of catheters.

Peritoneal catheters: 2 mg in 8 mL NS was infused via IP catheter to aid in drainage of abdominal abscesses in a 4-week-old infant.[42] To clear peritoneal dialysis catheter occlusions, a case series of six patients ages 3 weeks to 15 years old reported using 2 mg in 40 mL NS instilled for 1 hour then aspirated; this approach was successful in four of seven attempts.[43] A newborn received 4 mL of a solution of 1 mg/mL as a dwell for 2 hours to clear a peritoneal dialysis catheter. This approach was successful on two different occasions and prevented surgical catheter replacement.[44]