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Drug Shortage Alert
Thrombolytics
June 2023

Recommendations and information provided in this Drug Shortage Alert are compiled by experts in the field. Practitioners are advised to consult with their institution's staff to ensure that response to any drug shortage is in line with internal policies and procedures.

INTRODUCTION

- This document serves as a resource for information on this current shortage and in the event of a future shortage. It addresses the impact on adult and pediatric patients by providing potential management strategies, pharmacotherapeutic considerations, and safety implications.
- Thrombolytics such as tenecteplase and alteplase are used for critical care conditions such as acute ischemic stroke (AIS), pulmonary embolism (PE), and ST elevation myocardial infarction (STEMI).
- Both tenecteplase and alteplase are on shortage due to increased global demand and challenging manufacturing processes.
- Alteplase should be reserved for acute PE because of the literature supporting increased efficacy whereas both alteplase and tenecteplase can be used for treatment of AIS.
- The recommendations provided in this document are based on both current evidence, including a review of available literature by the SCCM Drug Shortages and Medication Safety Committee, and the need for conservation during this shortage.

MANAGEMENT STRATEGIES

- Depending on institution supply, consider reserving alteplase and tenecteplase for AIS since there are no other approved therapeutic options for this indication.
- Alteplase is FDA-approved for AIS, PE, and STEMI. Tenecteplase is FDA-approved for STEMI. Based on recent clinical trials, tenecteplase can be used off-label for AIS and PE [1-6].
- Conservation strategies to reduce waste include:
  - Using alteplase for catheter clotting
  - Setting aside and not disposing out-of-date thrombolytics, pending further decisions on potential expiration date extensions
  - Centralizing thrombolytic supply in one area of the pharmacy department to ensure efficient use
  - Choosing appropriate vial sizes to avoid waste
  - Avoiding stockpiling supply to allow patients across the country access timely treatment when indicated
- Using streptokinase and urokinase as alternative treatments for acute PE, although they are no longer available in the United States.
- Using reteplase for STEMI; it is FDA approved and has been studied for PE.

- See **Table 1** for more details on potential management strategies.

Table 1. Potential Management Strategies for Thrombolytic Shortages[1-14]

Indication	Suggested strategies
AIS	• Consider either alteplase or tenecteplase
PE	• Consider full dose or half-dose alteplase or tenecteplase, in appropriate situations ○ Current data better support alteplase for this indication • Can consider reteplase based on results from clinical trials
STEMI	• Alteplase, tenecteplase, and reteplase are FDA approved for STEMI ○ Primary percutaneous coronary intervention (PCI) is preferred, but fibrinolytics may be given if PCI is not available or feasible • Consider reteplase

AIS, acute ischemic stroke; PE, pulmonary embolism; STEMI, ST elevation myocardial infarction.

PHARMACOTHERAPEUTIC CONSIDERATIONS [1-6; 14]

- Although alteplase is the only thrombolytic FDA-approved for AIS, PE, STEMI, a growing number of studies have shown the efficacy and safety of tenecteplase for AIS and PE as well
  - The 2019 revision to the American Heart Association/American Stroke Association AIS guidelines state that tenecteplase can be used over alteplase.
  - This recommendation arose as a result of the EXTEND-IA TNK trial and the ACT trial that demonstrated that tenecteplase is noninferior to alteplase in the incidence of cerebral hemorrhage and functional outcomes, respectively.
- Alteplase:
  - For certain patients, use of half-dose alteplase (50 mg) for thrombolysis for submassive or massive PE may provide similar efficacy with reduced bleeding risk, compared to full-dose therapy (100 mg). Retrospective studies have demonstrated that half-dose was associated with similar mortality and bleeding rates.
- Tenecteplase:
  - Modifications at three molecular sites are engineered to give tenecteplase higher fibrin specificity and enhanced resistance to plasminogen activator-1; they also give tenecteplase a longer half-life compared to alteplase.
  - The complex administration of bolus plus continuous infusion of alteplase and its relatively short half-life are disadvantages of alteplase. Tenecteplase has a longer half-life, and it can be administered as a bolus, mitigating the need for a 60-minute thrombolytic infusion.
- Reteplase:
  - An observational study evaluated the use of reteplase in 40 patients with PE. Two bolus doses of reteplase, 10 mg, administered 30 minutes apart, along with an IV bolus of heparin 5000 units followed by heparin infusion (activated partial thromboplastin time 2-2.5 × normal) or therapeutic enoxaparin (1mg/kg subcutaneously twice daily) was administered 6 hours after the second bolus of reteplase. This regimen was effective in the treatment of submassive and massive PE with minimal risk of bleeding.
  - Data evaluating the use reteplase for the management of PE are limited to case reports, case series, and one observational study.
- See **Table 2** for more details on potential management strategies.

Table 2. Comparison of Alteplase, Tenecteplase, and Reteplase for Systemic Administration[1-15]

Characteristic	**Alteplase**	**Tenecteplase**	**Reteplase**
Mechanism of action	Catalyzes cleavage of plasminogen to plasmin, resulting in fibrin degradation and clot dissolution		
	Second-generation agent	Third-generation agent	Third-generation agent
Indications	Labeled for AIS, PE, STEMI	Labeled for STEMI Off-label: AIS, PE	Labeled for STEMI
Doses	**PE**: • 100 mg IV infused over 2 hours • Off-label dosing: 50 mg IV infused over 2 hours • PE + cardiac arrest (without pulse): 50 mg IV push over 2 minutes, repeat dosing 30 minutes later if no ROSC (small, nonrandomized studies have used variable dosing) **STEMI:** • **Patient weight ≤67 kg**: Infuse 15 mg IV bolus over 1 to 2 minutes, followed by infusions of 0.75 mg/kg (not to exceed 50 mg) over 30 minutes, then 0.5 mg/kg (not to exceed 35 mg) over 1 hour (maximum total dose: 100 mg) • **Patient weight >67 kg**: Infuse 15 mg IV bolus over 1 to 2 minutes, followed by infusions of 50 mg over 30 minutes, then 35 mg over 1 hour (maximum total dose: 100 mg) **AIS:** • **Recommended total dose: 0.9mg/kg (maximum total dose: 90 mg)**	**PE:** Administer dose as a single IV bolus over 5 to 10 seconds patient weight <60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg **STEMI**: Administer as a single IV bolus over 5 seconds: Patient weight <60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg **Acute ischemic stroke:** 0.25 mg/kg IV bolus (maximum 25 mg)	**STEMI:** 10 units IV over 2 minutes, followed by a second dose 30 minutes later of 10 units IV over 2 minutes

	• **Patient weight <100 kg:** 0.09 mg/kg (10% of 0.9 mg/kg dose) as an IV bolus over 1 minute, followed by 0.81 mg/kg (90% of 0.9 mg/kg dose) as a continuous infusion over 60 minutes • **Patient weight ≥100 kg**: 9 mg (10% of 90 mg) as an IV bolus over 1 minute, followed by 81 mg (90% of 90 mg) as a continuous infusion over 60 minutes		
Half-life	5 minutes	20-24 minutes	13-16 minutes
Administration	PE: IV infusion; IV bolus over 2 minutes (with cardiac arrest) STEMI or AMI: Bolus over 1 minute followed by infusion	Single IV bolus over 5 seconds Not compatible with D5W	IV bolus over 2 minutes
Monitoring	CBC, aPTT, signs and symptoms of bleeding, neurologic assessments, blood pressure		
Adverse effects	Bleeding, hypotension, allergic reactions, angioedema, anaphylactic shock, and reperfusion arrhythmias (in AMI)		
Average wholesale price per unit[15]	50 mg: $5,280 100 mg: $10,560	50 mg: $8,853	10 units: $4,071 20 units: $6,576

AIS, acute ischemic stroke; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; CBC, complete blood count; PE, pulmonary embolism; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction.

SAFETY IMPLICATIONS

- Having more than one fibrinolytic on the hospital formulary and stocked in the same dispensing area can increase the risk for medication errors. If multiple fibrinolytics are on the hospital formulary, supply should be separated, and clearly labeled.
    - For example, if only one particular thrombolytic is used for AIS, consider storing only that thrombolytic in the area where these patients are managed. If tenecteplase is used for AIS, consider removing the vials from the manufacturer carton that contains STEMI dosing. Pharmacy personnel should prepare each dose when possible to decrease chances for error by clinicians who are not familiar with these drugs.
- Order sets in electronic health records should be clear and should guide clinicians to pick the correct drug, dose, and administration time based on indication. Hospital guidance should be made outlining doses, administration techniques, and monitoring for each indication and drug. Routine education with bedside clinicians, including pharmacists, should be conducted accordingly.

- Tenecteplase dosing for STEMI is different from dosing for AIS. Patients with AIS can potentially receive a twofold overdose if accidently administered the dose for STEMI.
- Tenecteplase:
    - The package insert for tenecteplase includes the indication for STEMI but not for AIS. The inside flap of the tenecteplase carton made by the manufacturer says that the product is labeled for STEMI and provides STEMI dosing. This has the potential to cause confusion if clinicians use it for AIS.
    - Tenecteplase may be referred to by the popular abbreviations TNK or TNKase, which are similar to the abbreviations t-PA or TPS used for alteplase. This has led to confusion and mixups. The drugs should be referred to by their generic names instead of brand names, and abbreviations should be avoided in all verbal and written communications including order sets, automatic dispensing cabinets, electronic health records, smart pumps, and barcoding systems.

IMPACT ON ICU CARE

- An institutions may have only one thrombolytic available on formulary, or it may be in the process of switching from alteplase to tenecteplase to simplify dosing for AIS and STEMI.
    - This may affect availability and familiarity with these agents.
    - Dosing of each of the thrombolytics is different, which may increase the risk of medication errors and poor patient outcomes.
    - Many indications and doses are off-label; continued evaluation of high-quality evidence is necessary. Limited data exists supporting the use of particular fibrinolytics for situations (e.g., randomized controlled trials are lacking to support the use of tenecteplase and reteplase for the management of PE).
- Clear and constant communication (e.g., clinical decision support, email) is recommended to provide clinicians necessary information on how to appropriately prescribe these medications.
- Multiprofessional groups should be created to develop appropriate drug shortage mitigation strategies, including available drugs on formulary and appropriate education.
- Education of staff and caregivers is necessary to limit potential risks to patients.

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