



Pharmacy Friday

Brief pearls related to acute care pharmacology and evidence-based medicine

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Thrombolytics in Submassive Pulmonary Embolism

Introduction

1. Pulmonary embolism (PE) is a disease with significant morbidity and mortality, with an annual incidence of 100,000 cases in the U.S.
2. Clinical presentation varies, with up to 25% of patients experiencing sudden death, while other patients with large thrombus burden experiencing few symptoms.
3. There are various methods to define a patient with pulmonary embolism such as massive PE (SBP <90) or submassive (signs/ symptoms of RV strain).
4. Evidence is controversial on the method, route, dose, and indication to administer fibrinolytics in submassive PE, leaving medical providers in difficult predicaments when patient suddenly become more ill on exam.

Pharmacology

Properties	Alteplase	Tenectapase
Dose	IV: 10 mg over 1 min then remaining 50-100 mg over 2 hours IA: 1 mg/hr intra-arterially for 24 hours	<60 kg: 30 mg 60-69 kg: 35 mg; 70-79 kg : 40 mg 80-89 kg: 45 mg; >90 kg: 50 mg
Administration	IV infusion or ultrasound guided	IV push over 10 seconds
Formulation	Intravenous	Intravenous
PK/PD	½ Life: 5 mins; terminal ~60 mins Metabolism: Degraded to constituent amino acids Excretion: Not impacted by renal or hepatic function	½ life: 20-24 mins; terminal 90-130 mins Metabolism: Degraded to constituent amino acids Excretion: Not impacted by renal or hepatic function
Adverse Effects	Bleeding, angioedema (more likely if on ACEI prior to admission)	Bleeding
Monitoring and warnings	Fibrinogen, apt/Anti-Xa, Hemoglobin, platelets	Fibrinogen, apt/Anti-Xa, Hemoglobin, platelets
Compatibility	Incompatible with heparin, bivalirudin, cangrelor, dopamine	Not tested against other product, cautious with Y site other drugs
Location in GHS	Zone 2+3 pyxis, CT scan, Trauma	Non-formulary
Comments	Fibrin Specificity ++	Fibrin Specificity +++

Warning/Contraindications

Strong Considerations	Mild to Moderate Considerations
<ul style="list-style-type: none"> • History of cerebrovascular accident • Recent intraspinal or intracranial trauma or surgery • Active internal bleeding • Severe uncontrolled hypertension • Known bleeding diathesis • Intracranial neoplasm, aneurysm, or arteriovenous malformation 	<ul style="list-style-type: none"> • Age >75 years • Pregnancy • Uncontrolled hypertension • Recent internal bleeding (non-intracranial) • Recent trauma, including traumatic CPR • Diabetic retinopathy • Recent surgery or invasive procedure • Pericarditis Ischemic stroke (>3 months prior) • Patients currently receiving oral anticoagulation (eg, warfarin)

Early Mortality Risk		Risk Parameters and Scores			
		Shock or Hypotension	PESI Class III-V or sPESI ≥1	Signs of RV Dysfunction on an Imaging Test	Cardiac Laboratory Biomarkers
High		+	+	+	+
Intermediate	Intermediate-high	-	+	Both Positive	
	Intermediate-low	-	+	Either 1 (or none) positive	
Low		-	-	Assessment optional: if assessed, both negative	

Overview of Evidence			
Author, year	Design/ sample size	Intervention & Comparison	Outcome
Kiser, 2018	Cohort/n=3768	Alteplase 50 mg vs. Alteplase 100 mg	<ul style="list-style-type: none"> • 50 mg associated with: <ul style="list-style-type: none"> ◦ ↑ secondary thrombolysis, catheter thrombus fragmentation, and total cost • No difference in bleeding or mortality
Arora, 2017	Cohort/ n= 4,426	Systemic thrombolysis vs. Catheter-directed thrombolysis (CDT)	<ul style="list-style-type: none"> • ↓ In-hospital mortality, 30 day readmission with CDT • ↓ GI bleed with CDT and ↑ cost by \$ 5798
PEITHO, 2016	RCT/ n=1006	Tenecteplase 30-50 mg + UFH vs. Placebo + UFH	<ul style="list-style-type: none"> • ↓ Death or hemodynamic collapse with TNKase • ↑ Major Bleeding (11.5% vs 2.4) <ul style="list-style-type: none"> ◦ Increased risk in > 75 years old • ↑ ICH (2% vs 0.2%)
Chen , 2014	Meta-analysis/ n=1247	Thrombolytics vs. Anticoagulation	<ul style="list-style-type: none"> • Significant ↓ in recurrent PE or death (OR = 0.37) • Significant ↑ in non-major bleeding (OR = 4.12) • No difference in major bleeding
MOPETT, 2013	RCT/ n=121	Alteplase 50 mg + UFH/LMWH vs. Placebo + UFH/LMWH	<ul style="list-style-type: none"> • ↓ Pulmonary hypertension with alteplase <ul style="list-style-type: none"> ◦ 16% vs. 57%; (NNT= 2) • ↓ LOS in alteplase group and no bleeding in both groups
MAPPET-3, 2002	RCT/ n=256	Alteplase 100 mg + UFH vs. Placebo + UFH	<ul style="list-style-type: none"> • No difference in mortality • Heparin alone= ↑ deterioration <ul style="list-style-type: none"> ◦ (24.6% vs 10.2%; p = 0.004) • No change in bleeding between the groups

References

1. Micromedex [Electronic version]. Greenwood Village, CO: Truven Health Analytics. Retrieved September 6, 2018, from <http://www.micromedexsolutions.com/>
2. Kiser TH, et al. Half-Dose Versus Full-Dose Alteplase for Treatment of Pulmonary Embolism. *Crit Care Med*. 2018 Oct;46(10):1617-1625.
3. Arora S, et al. Comparison of In-Hospital Outcomes and Readmission Rates in Acute Pulmonary Embolism Between Systemic and Catheter-Directed Thrombolysis (from the National Readmission Database). *Am J Cardiol*. 2017 Nov 1;120(9):1653-1661
4. Meyer G, et al., PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402-11.
5. Chen H, et al. Thrombolysis versus anticoagulation for the initial treatment of moderate pulmonary embolism: a metaanalysis of randomized controlled trials. *Respir Care* 2014;59: 1880-7.
6. Kline J. et al. "Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial." *J Thromb Haemost*. 2014. 12(4):459-468.
7. Konstantinides S, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143-50
8. Sharifi M, "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol* 2013;111: 273-7.
9. Long B, et al. Current Controversies in Thrombolytic Use in Acute Pulmonary Embolism. *J Emerg Med*. 2016 Jul;51(1):37-44.