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The Use of Thrombolytics for ACS

Introduction

1. Percutaneous coronary intervention (PCI) is the preferred reperfusion strategy during a cardiac arrest; thrombolytic therapy is an option without PCI capability, followed by transfer to a PCI capable center.
2. Thrombolytic therapy is most effective when administered within 30 minutes of first medical contact, however, may be considered within 12 – 24 hours of symptom onset and ongoing ischemia or extensive ST elevation.
3. During ACS-Induced Cardiac Arrest, the goal for fibrinolysis is 30 minutes and reperfusion with PCI is preferred, however, if PCI is delayed, fibrinolytics therapy could be considered.

Pharmacology		
	Alteplase	**Tenecteplase**
MOA	Initiates fibrinolysis by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin	Promotes initiation of fibrinolysis by binding to fibrin and converting plasminogen to plasmin; similar to alteplase but more fibrin specific
Dose	Weight based: > 67kg: infuse 15mg IV bolus over 1-2 minute, followed by 50mg infusion over 30 minutes, then 35mg over 1 hour (max total dose 100mg) ≤ 67kg: : infuse 15mg IV bolus over 1-2 minutes, followed by 0.75mg/kg infusion over 30 minutes, then 0.5mg/kg over 1 hour (max total dose 100mg)	Weight based: < 60kg: 30mg ≥ 60 to < 70kg: 35mg ≥ 70 to < 80kg: 40mg ≥ 80 to < 90kg: 45mg ≥ 90kg: 50mg
Administration	• Bolus administered over 1 minute followed by infusion	• Single bolus over 5 seconds
PK/PD	**Duration**: 1 hour after infusion terminated **Distribution**: approximates plasma volume **Half-life elimination**: 5 minutes **Excretion**: hepatic and plasma clearance	**Distribution**: weight related **Metabolism**: hepatic **Half-life elimination**: biphasic; initial 20-24 min, terminal 90-130 min **Excretion**: plasma clearance
Adverse Effects	• Intracranial hemorrhage • Ecchymosis • GI/GU hemorrhage • Sepsis • Cerebrovascular accident	• Hemorrhage and hematoma • Cerebrovascular accident
Drug Interactions and Warnings	• Tranexamic acid, avoid combination • Internal bleeding, thromboembolic events, cholesterol embolization	• Tranexamic acid, avoid combination • Internal bleeding, thromboembolic events, arrhythmias
Contraindications	• Active internal bleeding • Ischemic stroke within 3 months except when within 4.5 hours • Severe uncontrolled hypertension	• Active internal bleeding • Severe uncontrolled hypertension • Recent intracranial/intraspinal surgery • Ischemic stroke within 3 months
Compatibility	May be diluted in equal volume with: • 0.9% sodium chloride • D5W	• Incompatible with dextrose

Overview of Evidence			
Author, year	**Design/ sample size**	**Intervention & Comparison**	**Outcome**
Guillermin 2016[a]	Meta-analysis of RCT (n=18,208)	• Tenecteplase 30-50mg vs alteplase 80-100mg	• Bleeding 4.8% in tenecteplase vs 5.8% alteplase (p=0.0002) • No difference in mortality at 30 days
Llevadot 2001	Retrospective review (38 studies)	• Reteplase • Anoteplase • Tenecteplase	• Tenecteplase and reteplase associated with accelerated infusion and more convenient by bolus administration • Administration of a less fibrin-specific agent may cause greater systemic coagulopathy with potential for more bleeding
Boersma 1996	Retrospective review (n=50,246)	• Fibrinolytic therapy vs placebo	• Mortality reduction in patients treated within 2 hours compared to later (p=0.001)
GUSTO 1993	Randomized, controlled trial (n=41,021)	• Streptokinase + SQ heparin • Streptokinase + IV heparin • Alteplase + IV heparin • Alteplase + Streptokinase + IV heparin	• Atleplase administered over 1.5 hours with IV heparin provide survival over standard therapy • Thrombolytic therapy administered within 24-48 hours of admission
Armstrong 2013[b]	Randomized controlled trial (n=1892)	• PCI vs bolus tenecteplase, clopidogrel, and enoxaparin	• Tenecteplase administration prehospital resulted in effective reperfusion when PCI was not completed within 1 hour • Fibrinolytic therapy associated with increase risk of intracranial bleeding
Cardiac Arrest Data			
Bottiger 2001	Prospective cohort (n=40)	• Alteplase 50 mg bolus, repeat 50 mg in 30 minutes vs placebo	• Increase in ROSC (68% vs 44%), ICU admission compared to placebo
Schreiber 2002	Retrospective chart review (n=157)	• Alteplase 15mg bolus followed by 50mg infusion over 30 min and 35mg over 60 min	• Thrombolytic therapy achieved better functional neurological recovery more frequently (p=0.03)
Lederer 2004	Retrospective chart review (n=108)	• Alteplase 100 mg (15 mg followed by 85 mg over 90 min)	• 81% of patients who received thrombolytic therapy were discharged without neurological deficit • 67% of patients were still alive 5-10 years after the event
Li 2006	Meta-analysis	• Alteplase 15mg bolus followed by 50mg infusion over 30 min and 35mg over 60 min	• Thrombolytic therapy improved the rate of ROSC ($p < 0.01$) • 48% of patients had acute coronary artery obstruction
Bottiger 2008	Randomized, double-blind, multicenter trial (n=1050)	• Tenecteplase 30mg if < 60kg • Tenecteplase 35mg if 60-69kg • Tenecteplase 40mg if 70-79kg • Tenecteplase 45mg if 80-89kg • Tenecteplase 50mg if > 90kg • Placebo	• No difference in tenecteplase and placebo in 30-day survival, ROSC, survival, or neurologic outcomes • Increased intracranial hemorrhages in tenecteplase patients
Ruiz-Bailen 2001	Retrospective cohort (n=303)	• Streptokinase • Alteplase accelerated regimen • Alteplase double bolus	• Systemic thrombolysis patients had a lower mortality, less mechanical ventilation, fewer CPR attempts ($p < 0.0001$) • No fatal hemorrhagic complications

[a]Administered as tenecteplase 30-50mg bolus and alteplase 15mg bolus followed by 0.75mg/kg infusion over 30 min
[b]Half-dose tenecteplase administered in patients ≥ 75 years old
[c]Reteplase administered as two boluses of 10 million units given 30 minutes apart

Conclusions

1. Evidence supports PCI is the first line option for management of patients requiring reperfusion during cardiac arrest when a STEMI is suspected
2. Available evidence suggests tenecteplase and alteplase are appropriate fibrinolytic therapies when PCI is unavailable
3. Tenecteplase is an alternative fibrinolytic therapy and has been evaluated safe and efficacious as a bolus dose of 30-50mg
4. When alteplase is the only fibrinolytic therapy available, there is data to support bolus therapy +/- a weight based infusion during cardiac arrest
5. Thrombolytic agents administered during CPR can improve the rate of survival but are associated with a risk of severe bleeding

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