Pharmacy Friday

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tPA for Thrombosis in Cardiac Arrest

Introduction

1. There are a limited number of medications which can be used to treat an acute thrombus.
2. Tissue Plasminogen Activators (tPA), such as alteplase and tenecteplase, are the mainstay of thrombolytic therapy.
3. Since the mid-1990s, numerous case reports and clinical trials have been published regarding the use of thrombolytic therapy in cardiac arrest, however there is conflicting evidence regarding results about benefit and outcomes.
4. The 2015 AHA guidelines recommend considering thrombolytic therapy for cardiac arrest due to PE.
5. A more recent review article recommended a standard dose for this indication but this is anecdotal based on a combination of studies. The clinical controversy includes route of administration, dose, and patient selection.

Pharmacology - Alteplase	
Dose	Various dosing strategies utilized in cardiac arrest- up to 100 mg max o 50 mg or 100 mg bolus over 1-15 min x 1 dose o 50 mg bolus followed by second 50 mg bolus 10-20 minutes later
Administration	IV as bolus dose or infusion
Mechanism of Action	Initiates fibrinolysis by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin
PK/PD	Duration: 80% cleared within 10min; some fibrinolytic activity persists for 1 hr $t_{1/2}$ = 5 min
Adverse Effects	Hemorrhage (Intracranial, GI, GU) Ecchymosis
Drug Interactions and warnings	Contraindications o Active bleeding o h/o recent stroke, spinal surgery, head trauma o Uncontrolled HTN Interactions o Antiplatelets (↑ bleeding) o Anticoagulants (↑ bleeding) o Nitroglycerin (↓ concentration of alteplase)
Compatibility	NOT compatible with o Dobutamine o Dopamine o Heparin o Nitroglycerin

References

1. Alteplase. [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved September 6, 2018, from http://www.micromedexsolutions.com/
2. Link MS. *Circulation*. 2015; 132[suppl 2]:S444–S464.
3. Bottiger BW. Lancet. 2001; 357:1583-5.
4. Abu-Laban RB. N Engl J Med. 2002; 346:1522–1528.
5. Janata K. Resuscitation. 2003; 57:49–55.
6. Fatovich DM. Resuscitation. 2004; 61:309–313.
7. Bottiger BW. N Engl J Med. 2008; 359:2651–2662.
8. Er, PLoS One. 2009; 4:e8323-8.
9. Sharifi M. Amer J Emerg Med. 2016; 34:1963-1967.
10. Peppard SR. Am J Health-Syst Pharm. 2018; 75:870-875.
11. Logan JK. Amer J Emerg Med 2014; 32:789-796.

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Overview of Evidence					
Author, year	Design/ sample size	Population	Intervention & Comparison*	Outcome	Comments
Bottiger, 2001	Prospective, observational n = 40	• Out of hospital arrest • Any rhythm • No ROSC after 15min	50mg alteplase + 5000units heparin • Repeat dose after 30min of CPR	*Bleeding:* 5% (not associated with tPA) *ROSC:* 68% tPA vs 44% no-tPA *Discharge:* 15% tPA vs 8% no-tPA	**tPA is safe & effective** for treatment of CA due to PE
Abu-Laban, 2002	Randomized, double blind, placebo controlled n = 117	• Out of hospital arrest • PEA rhythm • No ROSC after 3min	100mg alteplase infused over 15min	*ROSC:* 21.4% tPA vs 23.3% no-tPA *Discharge:* 0.9% tPA vs 0% no-tPA	**No different in rate of ROSC or hospital discharge**; possibly due to prolonged time to tPA infusion (35min)
Janata, 2003	Retrospective n = 36	• Out of hospital arrest	0.6-1 mg/kg, max 100mg	*Bleeding:* 25% tPA vs 10% no-tPA *ROSC:* 67% tPA vs 43% no-tPA *Discharge:* 19% tPA vs 7% no-tPA	**No association with prolonged CPR and bleeding** complications
Fatovich, 2004	Randomized, double blind, placebo controlled n = 19	• Out of hospital arrest • Any rhythm	50 mg tenecteplase	*ROSC:* 42% TNKase vs 6% no-TNKase *Survival to hospital admission:* 10% TNKase vs 6% no-TNKase *Discharge:* 5% TNKase vs 6% no-TNKase *Bleeding Events*: 0	TNKase **increased ROSC** in CA due to any cause, however **did not increase hospital discharge**
Bottiger, 2008	Randomized, double blind, placebo controlled n = 525	• Out of hospital arrest • Initial rhythm PEA/asystole OR VF/VT after ≤ 3 defibrillation attempts	Weight-based tenecteplase	*30-day survival:* 14.7% TNKase vs17% no-TNKase *ROSC:* 55% TNKase vs 54.66% no-TNKase *ICH*: 2.6% TNKase vs 0.4% no-TNKase	**No difference in 30-day survival** with use of thrombolytics in CA and **increased risk of ICH**; median time to thrombolytic therapy 18 minutes
Er, 2009	Retrospective n = 104	• In-hospital arrest • Any rhythm • Suspicion for PE	80.5 ±2.4mg alteplase (determined by rescue team)	*Bleeding*: 23% *ROSC:* 38.5% Time to tPA: 13.6 min ROSC vs 34.7min no-ROSC *Discharge:* 47.5% Time to tPA: 11min d/c vs 23min no-d/c	**Early tPA** is associated with better outcomes
Sharifi, 2016	Retrospective identification, prospectively followed n = 23	• In-hospital arrest • PEA rhythm + Confirmed PE	50mg alteplase over 1 min + 2000-5000 units heparin (no comparator group)	*Bleeding Events:* 0 *ROSC:* 96% *Discharge:* 91%	• 50mg/1min is safe and effective in PEA & PE • **Quicker admin of tPA may be beneficial** (6.5min)
Peppard, 2018	Retrospective n = 35	• CA due to confirmed or suspected PE	Various alteplase dosing strategies- bolus, infusion or bolus + infusion (no comparator group)	*Bleeding Events:* 5 Higher cumulative doses associated with higher bleeding risk *ROSC:* 49% Median time to ROSC: 25 min *Discharge:* 14%	• **Shorter time to ROSC** (15.1 min) **with bolus** dose of alteplase compared with infusion (46.4) or bolus + infusion (48 min); most common bolus dose 50 mg

*Compared with no thrombolytics unless specified

CA= cardiac arrest

Conclusions

- tPA for PE-induced cardiac arrest has been studied for over 20 years but there is still no clear answer on how to dose tPA.
- AHA Guidelines state that thrombolysis may be considered when cardiac arrest is suspected to be caused by a PE, but provides no recommendation on inclusion criteria, thrombolytic timing, drug or dose.
- Studies support rapid utilization of a thrombolytic in patients with confirmed or highly suspicious for a PE is beneficial.

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