

Expanding the Window for Administration of tPA in Ischemic Stroke

Background

Recombinant tissue plasminogen activator (tPA, alteplase [*Activase*]) has been used for several years to improve neurologic outcomes in patients with ischemic stroke.¹ The main trade-off of this benefit is a risk for intracranial bleeding. There's good evidence for a favorable risk-to-benefit ratio when tPA is given within three hours after the onset of stroke symptoms. However, this window sometimes results in exclusion of patients who would otherwise be eligible to receive tPA. Newer evidence helps strengthen the case for expanding the window to 4.5 hours for certain patients. This document reviews the evidence and new guideline recommendations for tPA in ischemic stroke.

Evidence for tPA at Three to 4.5 Hours

There's observational data from the SITS-ISTR (Safe Implementation of Thrombolysis in Stroke-International Stroke Treatment Registry) suggesting no difference in outcomes (intracerebral hemorrhage, mortality, and independence at three months) for patients who receive tPA within three hours after stroke symptoms compared to those who receive it between three and 4.5 hours after onset.²

There's also data from a meta-analysis of studies suggesting a significant improvement in outcomes for patients who receive tPA up to 4.5 hours after onset of stroke symptoms (although the benefit appears to diminish with time). The risk for death or hemorrhage in this analysis was not associated with the time of administration when tPA was given within 4.5 hours.³

The most recent study to support increasing the window for administration of tPA from three to 4.5 hours after the onset of symptoms in patients with ischemic stroke is called ECASS 3 (the European Cooperative Acute Stroke Study). It's a multicenter, placebo-controlled RCT that enrolled 821 patients.^{4,5}

ECASS 3 used the current guideline recommended dosing regimen of tPA. It's 0.9 mg/kg (maximum of 90 mg) for one dose, with 10% given as a bolus and the rest infused over one hour.⁵

Patients excluded from ECASS 3 were those with a baseline NIH Stroke Scale Score >25, current use of oral anticoagulants, or a history of stroke plus diabetes. Individuals over the age of 80 years were also excluded. Otherwise, the subjects in ECASS 3 were the same as those eligible to receive tPA for ischemic stroke according to current treatment guidelines.⁵

The median time to administration of tPA or placebo was about four hours.⁵

The primary efficacy outcome of disability at 90 days was classified as either favorable or unfavorable. It was significantly better in the treatment group compared to the placebo group (52.4% vs. 45.2%, odds ratio [OR] 1.34, 95% confidence interval [CI] 1.02 to 1.76, p=0.04). The incidence of symptomatic intracranial hemorrhage was significantly higher in the treatment group compared to the placebo group. Mortality in the treatment group and placebo group did not differ.⁵

Taking into consideration the data from ECASS 3, it's estimated that around half as many patients will benefit from treatment with tPA in the three to 4.5 hour window as will benefit from treatment within the three hour window. There does not appear to be an increase in the risk for harm (e.g., symptomatic intracranial bleeding or death) with the extended time period. When tPA is given between three and 4.5 hours after the onset of stroke symptoms, up to one in six patients will have a better outcome as a result of therapy, compared to one in 35 who will have a worse outcome because of therapy.⁵⁻⁷

Updated Recommendations

Based on this new data, the American Heart Association (AHA), the American Stroke

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Association (ASA), and the Canadian Stroke Strategy now recommend that tPA can be given up to 4.5 hours after onset of stroke symptoms in some patients.^{4,8}

The guidelines do not recommend administration of tPA after the three hour mark to patients who were not studied in ECASS 3 (e.g., age >80 years, current use of an oral anticoagulant, an NIH Stroke Scale score >25, or history of stroke plus diabetes). The reason for exclusion of these patients is that efficacy of treating with tPA any later than three hours after onset of stroke symptoms has not been established.^{4,5,8}

Some of the contraindications for the use of tPA, regardless of timing, include head trauma or stroke within the previous three months, uncontrolled hypertension (SBP of 185 mmHg or more, or DBP of 110 mmHg or more), and the use of oral anticoagulants with INR of more than 1.7.¹

Conclusion

Administration of tPA to certain patients with ischemic stroke between three and 4.5 hours after the onset of symptoms improves outcomes without compromising safety [Evidence level A; high-quality RCT].⁵ Treatment guidelines have been updated as a result of this data.⁴ However, continue to facilitate the quickest possible administration of tPA to patients with ischemic stroke. Better outcomes are more likely with earlier administration.

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In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

Cite this Detail-Document as follows: Expanding the window for administration of tPA in ischemic stroke. Pharmacist’s Letter/Prescriber’s Letter 2009;25(7):250717.

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