stroke is the third leading cause of death in the United States and is the leading cause of disability in the elderly. The estimated cost of stroke-related medical costs and disability for Americans in 2010 will be about $73.7 billion.1 Ischemic stroke, which occurs due to obstruction of a blood vessel that carries oxygen and nutrients to the brain, accounts for about 83% of all strokes. Hemorrhagic stroke, which occurs due to a ruptured blood vessel within the brain, accounts for about 17%.

Thrombolytic therapy is the only medical treatment option for acute ischemic stroke (AIS). While antiplatelet therapy with aspirin has been shown to decrease the risk of early recurrent stroke when initiated within 48 hours of ischemic stroke onset, it does not actually treat the stroke that has already occurred.2,3 I.V. alteplase (recombinant tissue plasminogen activator) is the only Food and Drug Administration (FDA)-approved thrombolytic agent for the treatment of AIS. Alteplase has been shown to decrease the percentage of patients disabled by a stroke. Until recently, the use of alteplase was only recommended within 3 hours of the onset of AIS symptoms. However, two clinical trials published in 2008 demonstrated that therapy with i.v. alteplase remains safe and effective when given 3–4.5 hours after AIS onset. Although FDA has not yet approved expanding the time interval to 4.5 hours for treatment with i.v. alteplase, the American Stroke Association recently published a statement recommending administration of alteplase in eligible patients 3–4.5 hours after symptom onset. There is clinical evidence supporting the safety and efficacy of i.v. alteplase administration to eligible patients who present within 4.5 hours of AIS symptom onset. Treatment with alteplase decreases the likelihood of disability from an AIS and is not associated with an increased rate of mortality. Expanding the time window for treatment with alteplase would likely increase the percentage of AIS patients who are able to receive alteplase and thus ultimately decrease the percentage of those left disabled from an AIS.

Conclusion. Evidence supports the safety and efficacy of i.v. alteplase administration to eligible patients within 4.5 hours of AIS symptom onset.

Index terms: Alteplase; Dosage schedules; Geriatrics; Injections; Stroke; Thrombolytic agents; Toxicity
The Clinical Consultation section features articles that provide brief advice on how to handle specific drug therapy problems. All articles are based on a systematic review of the literature. The assistance of ASHP’s Section of Clinical Specialists and Scientists in soliciting Clinical Consultation submissions is acknowledged. Unsolicited submissions are also welcome.

The extended time period recommended by the American Heart Association and the American Stroke Association are slightly more extensive than the criteria for those treated within 3 hours after stroke. These additional exclusion criteria are also listed in the appendix. This article reviews the current literature for the safety and efficacy of i.v. alteplase in patients 3–4.5 hours after ischemic stroke onset.

**Literature review**

A Medline search was performed using the keywords alteplase, tissue plasminogen activator, and stroke. Reference citations from all relevant review articles and clinical trial reports were also evaluated. Prospective clinical trials from the data sources published in English that evaluated i.v. alteplase therapy after 3 hours of AIS symptom onset were included in this review. Seven trials were evaluating the use of i.v. alteplase in patients with AIS after 3 hours of symptom onset were identified.

The European Cooperative Acute Stroke Study (ECASS) I, published in 1995, was the first large (n = 620), randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating the use of i.v. alteplase in AIS, with the majority of patients receiving treatment after more than 3 hours of symptom onset (mean time from stroke onset to treatment with alteplase, 4.4 hours).\(^8\) This study failed to find a significant treatment benefit of alteplase in the intent-to-treat population but did find a significant benefit of alteplase in the target population, as evidenced by a lower median modified Rankin Scale (mRS) score at 90 days (2 versus 3, p = 0.035). The mRS is a validated stroke scale that measures disability due to stroke from 0 (complete recovery to an asymptomatic state) to 6 (death). The dose of alteplase used in this study (1.1 mg/kg) was higher than that normally used for the treatment of AIS (0.9 mg/kg). However, the higher dose did not result in a significantly higher mortality rate at 90 days or a significantly greater rate of ICH in patients receiving alteplase than in those receiving placebo. Of note, protocol violations were identified in 109 patients from the target population analysis, and the most common protocol violation was major early infarct signs (n = 43).

The ECASS II was designed similarly to the ECASS I but evaluated a lower dose of alteplase (0.9 mg/kg) than that used in the ECASS I; this lower dose was chosen to match the NINDS study criteria.\(^10\) In this trial, more than 80% of the 800 patients received treatment 3–6 hours after symptom onset. Despite alterations in the study protocol, this trial also failed to demonstrate clear superiority of alteplase treatment. Although not statistically significant, more patients in the alteplase group than in the placebo group had a favorable outcome, defined as an mRS score of 0 or 1, at 90 days (40.3% versus 36.6%, p = 0.277). Symptomatic intracranial hemorrhage occurred in more patients in the alteplase group than in the placebo group (8.8% versus 3.4%, respectively), but 30-day and 90-day mortality rates were similar between the treatment groups. Overall, the efficacy and safety of alteplase in this trial were consistent with results from previous trials, including the NINDS trial.

The next large clinical trial evaluating the use of alteplase in AIS 3 hours after symptom onset was the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study.\(^11\) This trial was initially designed to assess the use of alteplase within 6 hours of symptom onset (part A)\(^12\); however, enrollment was halted after two years due to safety concerns about patients receiving alteplase 5–6 hours after symptom onset, also considering the fact that the percentage of patients who had a severe stroke (defined as a National Institutes of Health Stroke...
Figure 5. Echoplanar Imaging with 

time interval of 3–5 hours after AIS onset. It is important to note that this trial excluded patients over age 80 years and those with an NIHSS score of >25, which limits the generalizability of this study’s results in clinical practice.

The ECASS III, which was published within two weeks of the SITS-ISTR study, compared the outcomes of 418 patients treated with alteplase 3–4.5 hours after stroke onset with the outcomes of 403 patients given placebo.8 This trial found that patients treated with alteplase were significantly more likely to have a favorable outcome (mRS score of 0 or 1) than those treated with placebo (52.4% versus 45.2%, respectively; odds ratio, 1.34; 95% confidence interval, 1.02–1.76; p = 0.04). While the rate of symptomatic ICH was significantly greater in patients treated with alteplase (2.4% versus 0.2%, p = 0.008), it was similar to the rate seen in previous trials of patients treated with alteplase within 3 hours of symptom onset, including the NINDS trial. The all-cause mortality rate at 90 days was similar between those treated with alteplase and those treated with placebo (7.7% versus 8.4%, p = 0.68). Overall, the ECASS III showed that treatment with alteplase remains safe and effective when administered to AIS patients 3–4.5 hours after the onset of symptoms.

Discussion

Until recently, i.v. alteplase was much greater in the alteplase group than in the placebo group.12 A greater percentage of patients receiving alteplase than those receiving placebo had an improvement of >11 points in the NIHSS score from baseline to 90 days (44% versus 36%, p = 0.03). However, other endpoints were not significantly different, including all-cause mortality at 30 and 90 days. Fatal ICH occurred significantly more in alteplase-treated patients than in placebo-treated patients (3% versus 0.3%, p < 0.001). It was then decided to restart the ATLANTIS trial (part B) with the time interval changed to within 5 hours of symptom onset.8 The study was further modified a couple of years later to a time interval of 3–5 hours after AIS onset, and patients enrolled after this point formed the intent-to-treat population for the ATLANTIS study, which was also stopped prematurely due to an interim analysis that indicated treatment was not likely to be beneficial. A significantly higher percentage of alteplase-treated patients than placebo-treated patients had a 4-point improvement in their NIHSS score at 24 hours (40% versus 21%, p = 0.02); however, this early effect had disappeared by 30 days. Treatment with alteplase significantly increased the rate of symptomatic ICH (11% versus 0%, p < 0.001) and the mortality rate at 90 days (23% versus 7%, p < 0.01). Since the trial was stopped after only half the number of desired patients were enrolled (n = 142)12 and since 80% of the 547 patients received treatment between 4 and 5 hours after symptom onset,11 the study was underpowered to accurately evaluate the safety and efficacy of alteplase, especially for patients treated between 3 and 4 hours after AIS onset.

The objective of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), published in early 2008, was slightly different than that of the studies discussed above.13 This trial tested whether i.v. alteplase 0.9 mg/kg given 3–6 hours after AIS onset promoted reperfusion and attenuated relative infarct growth in patients who had a mismatch in perfusion-weighted magnetic resonance imaging (MRI) and diffusion-weighted MRI, which is thought to signify an area of critically hypoperfused but viable brain tissue. The EPITHET investigators found that treatment with alteplase resulted in less relative infarct growth and significantly increased reperfusion than did treatment with placebo (p = 0.001). While reperfusion was associated with significantly better neurologic outcomes (NIHSS score of 0 or 1 or at least an 8-point improvement from baseline, p < 0.0001) and functional outcomes (mRS score of 0–2, p = 0.01) at 90 days, the sample size (n = 101) was too small to determine superiority of alteplase on clinical outcomes. However, the results of this study provide evidence that the time window for thrombolyis treatment might be extended beyond 3 hours in some patients.

The Safe Implementation of Treatments in Stroke—International Stroke Thrombolyis Registry (SITS-ISTR) was the first of two recently published studies that found i.v. alteplase to be safe and effective in AIS patients when given between 3 and 4.5 hours after symptom onset.7 This study was a prospective, Internet-based audit of more than 700 clinical centers in Europe that compared 664 patients treated with i.v. alteplase 0.9 mg/kg 3–4.5 hours after symptom onset with 11,865 patients treated within 3 hours of symptom onset. This observational study found that after three months of treatment, patients receiving alteplase in both groups experienced similar rates of functional independence (mRS score of 0–2) (58% of patients treated 3–4.5 hours after symptom onset versus 56.3% of those treated within 3 hours, p = 0.42) and excellent recovery (mRS score of 0 or 1) (40.5% versus 39.9%, $p = 0.79$) and did not differ in the incidence of symptomatic ICH (2.2% versus 1.6%, $p = 0.24$) or mortality (12.7% versus 12.2%, $p = 0.72$). Since about 70% of patients treated 3–4.5 hours after symptom onset were treated within the first 30 minutes of the time interval, these results may not be powered to determine the efficacy of alteplase toward the end of this extended time period. However, the study still showed that treatment with alteplase after AIS remains beneficial when given 3–4.5 hours after symptom onset.
only recommended for use within 3 hours of symptom onset of AIS.\(^2\)\(^4\) However, the results of two large clinical trials published in 2008 clearly demonstrated the efficacy and safety of i.v. alteplase 3–4.5 hours after the onset of ischemic stroke symptoms.\(^7\)\(^8\) The first three large clinical trials that evaluated the use of i.v. alteplase in AIS more than 3 hours after symptom onset, all published in the 1990s, failed to find clear benefit of its use.\(^9\)\(^11\) The inability of these trials to show a benefit is thought to be due to their lack of statistical power, a time window for treatment of up to 6 hours, and their choice of endpoints. However, with the exception of the ATLANTIS trial, which was significantly underpowered to accurately evaluate a treatment difference, none of these trials found excess detriment from the use of alteplase in this extended time interval. While treatment with alteplase is usually associated with an increased risk of symptomatic intracranial hemorrhage, it does not seem to increase the rate of mortality. Based on the clinical evidence from the two most recent trials, the science advisory statement recently published by the American Heart Association and the American Stroke Association recommended expanding the window for administration of alteplase to eligible patients to within 4.5 hours of AIS symptom onset.\(^6\)\(^8\) This expanded time period for i.v. administration of alteplase in patients with AIS has not yet been evaluated by FDA; therefore, alteplase is still only approved for use within 3 hours of AIS onset. It is important to keep in mind that extending the time period during which alteplase may be given to 4.5 hours should not slow efforts to facilitate rapid administration of i.v. alteplase to eligible patients experiencing AIS. It is hoped that by extending the time period for administration of i.v. alteplase, the percentage of ischemic stroke patients who are able to receive thrombolytic therapy will increase, ultimately decreasing the percentage of patients left permanently disabled from an ischemic stroke.

Evidence from additional large, prospective, randomized, placebo-controlled clinical trials would be helpful in solidifying the clinical role of i.v. alteplase administered 3–4.5 hours after the onset of AIS. Future research should focus on comparing the efficacy and safety of alteplase when given within 3 hours of AIS onset and when given 3–4.5 hours after onset. Primary outcomes should include the rate of excellent recovery (mRS score of 0 or 1) at 90 days, the rate of symptomatic ICH, and the mortality rate at 90 days. Until additional clinical trials have been completed, the decision to use i.v. alteplase in patients 3–4.5 hours after AIS onset should be guided by recommendations made by the American Heart Association, the American Stroke Association, and clinical expertise.

**Conclusion**

Evidence supports the safety and efficacy of i.v. alteplase administration to eligible patients within 4.5 hours of AIS symptom onset.

References


Appendix—Inclusion and exclusion criteria for thrombolytic treatment with alteplase in acute ischemic stroke (AIS)\(^1\)\(^4\)\(^8\)

**Inclusion criteria**

Age of ≥18 years

• Clinical diagnosis of ischemic stroke

• Onset of stroke symptoms within previous three hours

• Baseline computed tomography (CT) or magnetic resonance imaging (MRI) showing no evidence of intracerebral hemorrhage (ICH)

**Exclusion criteria**

• Minor or rapidly improving stroke symptoms

• Evidence of ICH on pretreatment evaluation (via CT or MRI)

• History of ICH, arteriovenous malformation, or aneurysm

• High clinical suspicion of subarachnoid hemorrhage even if CT scan is normal

• Witnessed seizure at stroke onset

• Intracranial surgery, serious head trauma, or previous stroke within previous three months

\(\geq\)
• Major surgery or serious trauma within two weeks
• Active internal bleeding (including any gastrointestinal or genitourinary bleeding) within previous three weeks
• Systolic blood pressure of >185 mm Hg or diastolic blood pressure of >110 mm Hg
• Serum glucose of <50 or >400 mg/dL
• Arterial puncture at a noncompressible site or lumbar puncture within previous week
• Platelet count of <100,000/mm³
• Administration of heparin within 48 hours and elevated activated partial thromboplastin time
• Current use of oral anticoagulants and an International Normalized Ratio (INR) of >1.7
• Recent acute myocardial infarction (or clinical presentation suggesting postmyocardial infarction pericarditis)
• Currently pregnant

Additional exclusion criteria for patients treated 3–4.5 hours after AIS symptom onset
• Age of >80 years
• Current use of oral anticoagulants (regardless of INR)
• Baseline National Institutes of Health Stroke Scale score of >20
• Medical history of both stroke and diabetes