When should patients with stroke receive thrombolytics?

■ EVIDENCE-BASED ANSWER

Thrombolytic therapy should be limited to patients with acute ischemic stroke who meet strict inclusion and exclusion criteria (Table) and who can adhere to strict treatment protocol. Patients treated under these conditions have improved combined mortality and disability outcomes at 1 year when treated with recombinant tissue plasminogen activator (rtPA) (number needed to treat [NNT]=18; 95% confidence interval [CI], 11–56) (strength of recommendation [SOR]: B, meta-analysis of randomized controlled trials with significant heterogeneity).1

Treating patients with rtPA outside the strict protocols definitely increases morbidity and mortality (SOR: A). A recent meta-analysis1 on this topic and the Cochrane review1 of eligible studies found the statistical heterogeneity and lack of precision in the analyses bothersome. These authors believed additional data were needed to more precisely define the circumstances in which thrombolysis could be recommended, if ever, for acute ischemic stroke.

■ EVIDENCE SUMMARY

The 2003 American Heart Association guidelines recommend rtPA for acute ischemic stroke “for carefully selected patients” who also need crucial “ancillary care.”2 The evidence for these guidelines comes primarily from large double-blind placebo-controlled studies using rtPA. However, these studies—including NINDS,4 ECASS,6 and ATLANTIS6—differ in their dosing regimen, timing, and other exclusion criteria, and outcome measurements.

The NINDS study, often employed as a benchmark,3,5,6 used a slightly lower dose of rtPA than other studies and “required that no anticoagulants or antiplatelet agents be given for 24 hours after treatment and that blood pressure be maintained within prespecified values.”4 Patients were evaluated for inclusion according to strict criteria, similar to those shown in the Table.

Patients in research studies who were treated outside protocol guidelines, and patients treated in community hospitals, have not fared as well as the patients in NINDS. In Connecticut,7 a review of thrombolysis in acute ischemic stroke revealed protocol deviations in 67% of the patients treated. The number needed to harm (NNH) for death was only 4 (in other words, there was an additional patient death for every 4 patients treated with rtPA), and significant extracranial hemorrhage had an NNH of 8. In Cleveland,8 50% of patients treated had at least 1 major protocol violation, and the NNH for symptomatic intracranial hemorrhage was 6. A quality improvement program in the Cleveland area lowered protocol violations to 19% and the NNH rose to 15.9

Improved outcomes similar to NINDS have been noted where there are stroke units or teams with personnel such as neurosurgeons, strict adherence to protocols, and facilities available to give accurate and expedient interventions and imaging (eg, neuroradiologic interpretations of CTs).1 These limits restrict the practical and safe use of rtPA to few of the millions of stroke victims.

The net positive outcome found in the Cochrane review1 results from subtracting the significant increase in symptomatic intracranial hemorrhage (NNH=16; 95% CI, 11–25) from the larger primary decrease in disability/death (NNT=10; 95% CI, 6–22).1 The overlapping confidence intervals of the outcomes was bothersome to the Cochrane reviewers.

■ RECOMMENDATIONS FROM OTHERS

Recommendations from the American Heart Association,2 the American Academy of Neurology,6
and the 6th American College of Chest Physicians Consensus Conference on Antithrombotic Therapy substantially agree. With minor variations, all recommend rtPA with inclusion/exclusion criteria similar to those outlined in the Table.

**Inclusion criteria**

Patient aged 26–79 years with a diagnosis of ischemic stroke, with consistent, measurable, new neurologic deficit that is not clearing spontaneously and causes impairment

Onset of symptoms ≤3 hours

Informed consent obtained from patient, appropriate family member, or power of attorney

Neuroradiologist and neurosurgeon on hand

Stroke unit or equivalent team/bed available

**Exclusion criteria**

Major neurological deficits

Onset of symptoms >3 hours before starting treatment

Head trauma or myocardial infarction in previous 3 months

Gastrointestinal or urinary tract hemorrhage in previous 21 days

Major surgery in previous 14 days

Arterial puncture at a noncompressible site in previous 7 days

History of intracranial hemorrhage

Blood pressure >185 mm Hg systolic or >110 diastolic at time thrombolytic therapy is given

INR >1.5

On heparin, or aPTT outside normal range

Platelet count <100K mm³

Blood glucose <50 mg/dL (2.7 mmol/L)

Seizure with postictal neurological impairments

Radiologic evidence that more than one third of cerebral hemisphere (by volume) is involved

Inability to maintain adherence to treatment guidelines

(Current aspirin use is not an exclusion criterion.)

| INR, international normalized ratio; aPTT, actived partial thromboplastin time |

**REFERENCES**

Is methylphenidate useful for treating adolescents with ADHD?

■ EVIDENCE-BASED ANSWER
Methylphenidate (Ritalin) is effective in the short-term treatment of attention deficit/hyperactivity disorder (ADHD) (strength of recommendation [SOR]: A, multiple randomized control trials).

Though the immediate-release preparation is the best studied of methylphenidate formulations, extended-release methylphenidate (Concerta) has similar benefits, with a dosing regimen that may better suit an adolescent lifestyle (SOR: B, based on extrapolation of 1 randomized controlled trial and expert opinion).

■ EVIDENCE SUMMARY
The subjects of most ADHD medication studies have been school-age children. Most children with ADHD will have symptoms persisting into teenage years, and methylphenidate has been increasingly prescribed for them. Various systematic reviews and meta-analyses have demonstrated the effectiveness of short-term methylphenidate in the treatment of adolescents with ADHD. Most participants in these studies are males aged <13 years. Therefore, any conclusions about the effectiveness of methylphenidate in older adolescents must be inferred.

The most comprehensive systematic review found 8 well-controlled crossover trials with an average sample size of 24.8 (range, 9–48). The average duration of the studies was 6 weeks. The majority of the participants were white males with a mean age of 13 years. Each study showed statistically significant improvement from treatment with methylphenidate. Average effect sizes were calculated for 3 domains: ADHD symptoms (0.94), social behavior (1.06), and academic performance (1.25). Effect sizes were calculated using a modified Cohen’s d, which is the difference between the treated and