MRI Buys Time for Thrombolysis of Acute Stroke

BY MITCHEL L. ZOLER
Philadelphia Bureau

New Orleans — The presence of a favorable pattern of cerebral perfusion on magnetic resonance imaging may tell physicians which patients with acute ischemic stroke stand to benefit from thrombolysis even hours after the onset of symptoms.

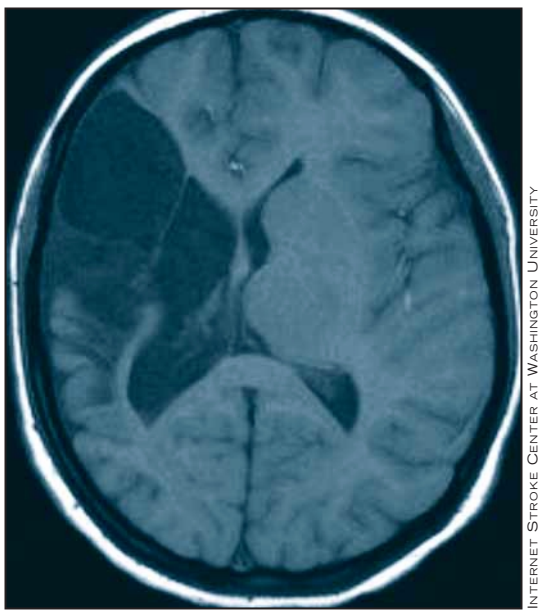
Findings from two phase II studies using MRI show that some patients were able to safely receive a thrombolytic drug as long as 9 hours after the onset of their stroke symptoms. Results from the most recent of these studies were reported at the 30th International Stroke Conference.

"These are the first trials to test the hypothesis that selecting patients with favorable imaging patterns can extend treatment beyond the current 3-hour window," said Anthony J. Furlan, M.D., head of the section of stroke and neurologic intensive care at the Cleveland Clinic and principal investigator of the new study. Results from the prior, European, study were published in January (Stroke 2005;36:66-73).

"If this hypothesis is borne out, it could have an enormous impact on how we use thrombolytic therapy for stroke," he added. "It has the potential to at least triple the number of acute stroke patients who are eligible for thrombolytic therapy."

Like the study done in Europe, Dr. Furlan's research used a combination of perfusion-weighted and diffusion-weighted imaging by MR to identify patients with at least a 20% mismatch between the two. The mismatch is a marker for patients with a significant penumbra region in their brain, tissue that might be salvageable by thrombolytic therapy because it is still viable despite being hypoperfused. "Most patients who made it to MR were eligible," he said.

The other novel feature of both the European and U.S. studies was the thrombolytic drug used: desmoteplase, a plasminogen activator derived from vampire-bat saliva. Desmoteplase has several potential advantages over tissue plasminogen activator (TPA). In animal studies, desmoteplase showed no neurotoxicity, and it did not activate β-amyloid, a process that's been linked to an increased risk of intracranial hemorrhage.



Internet Stroke Center at Washington University

A large infarct is clearly visible in the middle cerebral artery of an 18-year-old woman.

Desmoteplase also has very high specificity and selectivity for fibrin and a long serum half-life of 4 hours. This last property means that it can be given as a bolus dose and may also help prevent acute reocclusion of newly opened arteries.

Desmoteplase is being developed in the United States by Forest Laboratories and in Europe by PAION, a German drug company. Dr. Furlan is a consultant to both companies, and he received compensation from both for acting as a principal investigator in these and ongoing studies.

The U.S. study involved enrollment of 37 patients who all met the entry MR criteria. After randomization, 14 patients were treated with 90 mcg/kg desmoteplase, 15 received 125 mcg/kg desmoteplase, and 8 received placebo. The average time to treatment was 7 hours. Although patients could enter treatment as long as 9 hours after the onset of their stroke symptoms, the top reason for excluding patients from the study was that they had gone beyond the 9-hour window.

The U.S. study's primary end point was the rate of symptomatic, intracranial hemorrhage (sICH), which occurred in none of the patients. In the prior European study, one sICH occurred among 15 patients treated with 90 mcg/kg and none among 15 patients treated with 125 mcg/kg. Thus, the overall rate of sICH in these two studies at these two doses was 1 among 59 treated patients, a 1.7% rate that was lower than the 6% rate with TPA in routine practice, noted Dr. Furlan at the conference, sponsored by the American Stroke Association.

In the European study, 30 patients received substantially higher doses of desmotoplase, and they had a 27% rate of sICH. In this higher-dose group, the lowest desmotoplase dose associated with intracranial hemorrhage was 294 mcg/kg.

The new study was not powered to show significant differences in clinical outcomes. The reperfusion rate was 38% in the control group, 18% in the 90-mcg/kg group, and 53% in the 125-mcg/kg group. Improved clinical outcomes at 90 days were seen in 25% of those in the placebo group, 29% of those in the low-dose arm, and 60% of those in the high-dose arm. There was no reduction of safety or efficacy in the patients treated 6-9 hours after their stroke onset, compared with those treated 3-6 hours after onset. ■

Lower Dose of TPA May Suffice for Acute Stroke

BY MITCHEL L. ZOLER
Philadelphia Bureau

New Orleans — A lower-than-usual intravenous dose of tissue plasminogen activator may still be effective for treating patients with acute stroke, according to a review of 83 patients.

"A low dose of 0.6 mg/kg was safe and effective," Marilyn M. Rymer, M.D., and associates reported in a poster at the 30th International Stroke Conference.

The usual dose of intravenous tissue plasminogen activator (TPA) is 0.9 mg/kg, based on the regimen's safety and efficacy in the original thrombolytic therapy trial by the National Institute of Neurological Disorders and Stroke (NINDS) and reported in 1995, according to Dr. Rymer, medical director of the stroke center at Saint Luke's Hospital in Kansas City, Mo., and colleagues.

The idea of treating patients initially with a 0.6-mg/kg IV dose began with the Interventional Management of Stroke (IMS) trial, which reserved a 0.3-mg/kg dose for subsequent intraarterial delivery. Hospitals in the Mid America Brain and Stroke Institute (MABSI) regional network now routinely use the 0.6-mg/kg dose of intravenous TPA, and then send the patient by ambulance to a hospital or a referral center for further evaluation, Dr. Rymer and her associates reported in a poster at a conference sponsored by the American Stroke Association.

Dr. Rymer and her colleagues identified 83 patients who received the 0.6-mg/kg dose only in the MABSI database, as well as another 50 patients who received a 0.6-mg/kg dose initially that was later followed by intraarterial treatment with 0.3 mg/kg of TPA to assess in-hospital mortality and patients' NIH Stroke Scale (NIHSS) score at discharge. This analysis used a discharge NIHSS of 4 or less and 2 or less as criteria for good outcomes.

The in-hospital mortality rates were 6% in the 83 patients treated with 0.6 mg/kg of TPA only and 12% in all 133 patients in the MABSI database. The 90-day mortality rates were 17% in the original NINDS trial and 16% in the IMS trial.

At hospital discharge, 71% of the patients who received just the 0.6-mg/kg dose had an NIHSS of 4 or less, and 63% had a score of 2 or less. In the entire MABSI group, 62% had discharge scores of 4 or less and 48% had scores of 2 or less. In the NINDS and IMS studies, NIHSS were measured 90 days after treatment; 31% and 28% of patients, respectively, had scores of 1 or 0 at that time, the investigators reported. ■

Aspirin Is Better Than Warfarin for Intracranial Arterial Stenosis Patients

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

High-dose aspirin is just as effective as warfarin in treating intracranial arterial stenosis, and appears much safer, Marc Chimowitz, M.B., and colleagues have reported.

"The common practice of administering warfarin rather than aspirin for symptomatic intracranial arterial stenosis is not supported by the results of this trial," said Dr. Chimowitz of Emory University, Atlanta.

Enrollment in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial ended early because of the high rate of serious adverse events in the warfarin patients. In addition to being safer for patients, the researchers said, aspirin therapy did not require constant monitoring of international normalized ratios (INRs) and treatment of warfarin-associated bleeding. Aspirin also is much cheaper, they noted (N. Engl. J. Med. 2005;352:1305-16).

Ralph Sacco, M.D., an investigator in the Northern Manhattan Stroke Study, noted in an interview that the WASID trial's findings add to existing data to dispel beliefs about the benefit of warfarin for certain stroke populations.

The conclusion that warfarin provides no survival benefit over aspirin, but confers added risk, is more expensive, and requires intensive monitoring, should reshape its risk/benefit profile for some patients, said Dr. Sacco, professor of neurology and epidemiology at Columbia University, New York.

Dr. Chimowitz and his associates reported on the trial's final analysis that included 569 patients with symptomatic intracranial arterial stenosis who were randomized to either warfarin 5 mg daily or aspirin 650 mg twice daily.

The patients' mean age was about 63 years; about 61% were men. All had a history of either stroke or transient ischemic attack caused by 50%-90% stenosis of a major intracranial artery. The mean follow-up was 1.8 years.

The primary outcome—stroke, brain hemorrhage, or death from vascular causes other than stroke—occurred in 22% (62) of the aspirin patients and 21.8% (63) of the warfarin patients. Myocardial infarction or sudden death occurred significantly more often in the warfarin group than in the aspirin group (7.3% vs. 2.9%).

The overall rate of death was significantly higher in the warfarin group than in the aspirin group: 5.9% (17) vs. 4.3% (12). However, chance probably accounted for some of the deaths that were higher in the warfarin group, especially the six cancers. Major hemorrhages occurred significantly more often in the warfarin group (8.3% vs 3.2%).

Dr. Sacco noted that warfarin is "clearly indicated" for cardioembolic stroke. "This has been made clear in multiple studies, which were actually so positive that they were the springboard for these other studies looking at warfarin in different populations." ■

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