Adding to the Effectiveness of Intravenous Tissue Plasminogen Activator for Treating Acute Stroke

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Intravenous tissue plasminogen activator (rt-PA) remains the only approved therapy for acute ischemic stroke with demonstrated effectiveness in phase 3 clinical trials.1 Unfortunately, the utilization of this treatment is limited by a 6% risk of symptomatic brain hemorrhage2 and a brief 3-hour time window of efficacy from symptom onset to treatment.3 Furthermore, its effectiveness is limited for several reasons; intravenously administered rt-PA often fails to lyse large clots,4,5 arteries reocclude in about a third of cases,5 flow may remain stagnant in the microcirculation despite clot lysis,6,7 and cellular injury may continue despite reperfusion.8

Attempts to augment the effect of IV rt-PA have so far been only partially successful. The most promising results have occurred with endovascular techniques that deliver smaller doses of lytic drugs, energy-producing catheters, or mechanical devices directly into the clot to achieve more complete lysis. Pro-urokinase delivered directly into proximal occlusions of the middle cerebral artery on average 5.3 hours after stroke onset was able to achieve lysis in 66% of cases with improved outcome (over heparin alone) in a phase 2 trial.9 Similarly, if IV rt-PA is followed by intra-arterially administered rt-PA (average 3.6 hours after stroke onset), complete or partial recanalization occurred in 56% with improved outcome compared with historical placebo-treated controls.10 Both of these studies need replication with a larger sample and head-to-head comparison against IV rt-PA alone. Studies with various energy-producing and mechanical disruption catheters are just starting. All of these endovascular techniques have the limitations of expense, available expert manpower, and most importantly, time.

Antithrombotic therapies alone have not proven effective in acute stroke patients, and they do increase bleeding risk. To date, they have not been tested in conjunction with lytics. Heparin, low molecular weight heparins, and heparinoids have proven ineffective in acute stroke patients in recent trials,11–13 a study of the direct thrombin inhibitor Argatroban (GlaxoSmithKline) has just been stopped because of futility,14 and aspirin alone is of limited benefit.11,15 A phase 2 study of the glycoprotein IIb/IIIa receptor antagonist abciximab was reported at an international meeting in February 2003, and phase 3 studies are planned based on this preliminary safety study.16 Cytoprotective therapies targeting perturbed ion channels, activated neurotransmitter receptors, and inflammation after acute stroke have also been neutral or negative, but these drugs have only rarely been linked with lytics in a combined strategy.17

It is logical to consider combinations of therapeutic strategies for treating this difficult condition. It makes sense to link lytic therapy with antithrombotic drugs to augment and speed lysis, reduce reocclusion, and improve microcirculatory flow in the brain after ischemic stroke. If this could be achieved, we might expect better clinical outcomes in patients with large clots treated early, and, if faster lysis is achieved, perhaps benefit for those patients in whom treatment cannot occur until the end of the treatment window.

The study reported in this issue of Circulation by Zhang and colleagues18 demonstrating the benefits of combining IV rt-PA with a glycoprotein IIb/IIIa receptor antagonist supports this concept. Highlights of this study include a unique embolic stroke model in rats that is amenable to treatment with lytic drugs, a positive effect on both histological and behavioral outcomes when the drug combination was delayed until 4 hours after stroke (when neither treatment alone had an effect), no increase in bleeding compared with rt-PA alone, and confirmation of benefit on microcirculatory flow.

Combined with an earlier study from the same laboratory showing similar results with Argatroban,19 data have shown that it is time to move ahead with pilot human studies to see if these combined approaches will result in clinically meaningful benefit compared with IV rt-PA alone. This may be easier to detect in patients treated 2 to 4 hours after stroke onset when the benefit of IV rt-PA alone is less apparent and when most stroke patients who are eligible for early treatment arrive in the emergency department. Increased bleeding was not seen with the combination in these experimental studies, and in fact, when the rt-PA dose was reduced by 50% in the combination, there were no hemorrhages and clinical benefit was preserved. Despite these reassuring results, it will be essential to closely monitor bleeding complications in future stroke trials of any combination strategy.

References


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