Too Much Intraarterial TPA Impedes Clot Lysis

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OAHU, HAWAII — Inadvertent overdosing of ischemic stroke patients with tissue plasminogen activator can significantly undermine the drug's effectiveness, Buddy Connors, M.D., said at a meeting sponsored by the American Society of Interventional and Therapeutic Neuroradiology.

When tissue plasminogen activator (TPA) is administered for treatment of an acute ischemic stroke, the dose used for catheter-directed intraarterial fibrinolysis might be inadvertently 100-1,000 times the optimal dose.

Few interventionalists or stroke neurologists realize that when these relatively "massive" doses are given intraarterially by catheter-directed therapy, thrombolytic activity may actually be decreased by up to 90%, according to Dr. Connors, medical director of interventional neuroradiology at Baptist Cardiac and Vascular Institute in Miami.

Although intravenous alteplase initiated within 3 hours after the onset of stroke symptoms is the only TPA treatment approved by the Food and Drug Administration for acute ischemic stroke, recombinant TPA, such as alteplase and reteplase, are being used off label for intraarterial lysis in ischemic stroke.

To gain more accurate clinical information about dosing of intraarterial thrombolytic agents and stroke outcomes, Dr. Connors urged the audience members to contribute data to the Interventional Stroke Therapy Outcomes Registry (INSTOR) at www.strokeregistry.org.

In addition to TPA's direct neurotoxic effects, serious adverse events may result from overshooting the optimal dose. These can include increasing the risk of bleeding in the brain as well as remote areas such as the gums, gastrointestinal tract, retroperitoneum, or elsewhere, as well as direct interference with clot lysis.

This unintentional intraarterial overdosing has arisen because no dose-ranging studies have been done specifically for intraarterial TPA stroke therapy, Dr. Connors said.

Doses for TPA that are typically used for intraarterial stroke therapy were arbitrarily chosen to be "one-third" of the total dose that was proved effective for intravenous stroke therapy by the National Institute of Neurological Disorders and Stroke IV TPA stroke trials. This decision resulted in the very high intraarterial dose used in the later intraarterial trials.

The data proving this paradox in dosing were obtained from direct pharmacokinetic testing as well as in vivo testing, Dr. Connors noted. Both alteplase and reteplase demonstrate well-defined bell-shaped curves of fibrinolytic activity. At twofold higher or lower concentration, activity is reduced by 25%. At eightfold higher or lower concentration, activity is reduced by 50%, compared with the optimal dose. At 100 times the optimal dose, activity might be cut by as much as 90%.

Dr. Connors suggested the lytic capability for intraarterial thrombolysis with reteplase and alteplase are about equal and the optimal infusion concentrations should be about 1 U reteplase/100 cc normal saline infused at 0.1-1 U/hr and 1 mg/100 cc for alteplase infused at 0.1-1 mg/hr.

The optimal dosing for urokinase might be 250,000-500,000 U/hr for urokinase (mixed in 100 cc of normal saline). These concentrations are typically infused into stagnant blood, thus preserving the high concentrations of even these extremely low doses.

As explanation of these recommendations, first it is important to remember that TPA itself does not dissolve clot—plasmin does, Dr. Connors said. TPAs are catalysts for the reaction that turns plasminogen into plasmin. Fibrinolysis occurs when plasmin binds to a receptor on fibrin and then causes lysis of fibrin. High doses of TPA flood these receptors and block plasmin's ability to bind with these receptors on fibrin, thus interfering with fibrinolysis.

"Don't oversaturate the receptors on fibrin with TPA. You want to optimally catalyze plasminogen into plasmin and allow the plasmin to then reach these receptors on fibrin in order to cause lysis," Dr. Connors said.

Besides dose conservation, he said that intraarterial thrombolytic outcomes improve if therapy is started before the 3-hour mark but rarely beyond 7 hours (except in basilar artery thrombosis—a distinct entity of its own). ■