

Snake Venom to Aid Stroke Victims

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Brain attacks require rapid action to decrease the risk of death or long-term disability, yet current drug therapies limit interventions to within three hours of the start of symptoms. Scientists have developed an investigational agent, called ancrod (Viprinex), derived from the venom of the Malayan pit viper that offers the potential to extend the window of treatment opportunity.

"The main benefit [of ancrod] is there is a possibility for treatment up to six hours. That's why this trial is so important," says Anne Leonard, RN, BSN, MPH, CCRC, FAHA, stroke and cerebral vascular program coordinator for neurosurgery at the University of Texas Health Sciences Center at San Antonio. "The other benefit, and we won't know until the study is over, may be that the risk of bleeding will be less."

Stroke dangers

Each year about 700,000 people suffer a new or recurrent stroke - which means there is about one stroke every 45 seconds, according to the American Heart Association. In 2004, more than 150,000 people died due to a stroke. Stroke ranks third, behind heart disease and cancer, among all causes of death when considered separately from other cardiovascular diseases, and it is the leading cause of serious, long-term disability. The AHA estimates direct and indirect cost of stroke in 2007 will cost \$62.7 billion.

Approximately 87% of strokes are ischemic, caused by a clot blocking blood flow to the brain, with the balance resulting from intracerebral and subarachnoid hemorrhage. Improving blood flow through a blocked vessel to return oxygen and nutrients to the region supplied by the artery remains a key stroke-treatment strategy. Deprived of oxygen, brain tissue can die, leading to neurological deficits.

Currently, doctors can administer the thrombolytic agent tissue plasminogen activator (tPA), but it must be given within three hours of symptom onset. Yet, the median time that elapses between suffering a stroke and arriving at the hospital ranges between three and six hours, according to data from the heart association.

The recently released "Guidelines for the Early Management of Adults with Ischemic Stroke," from the AHA/American Stroke Association confirms that intravenous administration of tPA remains the most beneficial proven intervention, with best outcomes observed in patients receiving the drug within 90 minutes. The guidelines indicate that intra-arterial thrombolytic agents and mechanical interventions, such as endovascular procedures to extract clots, hold promise. The guidelines also mention ancrod and indicate that it should be only given as part of a clinical trial.

Ancrod's history

European and Canadian physicians first began using ancrod in the 1970s as a reperfusion therapy for peripheral vascular disease, deep vein thrombosis, and central retinal venous thrombosis, according to the article "Intravenous Ancrod in Acute Ischemic Stroke," published in May 2000 in *the Journal of the American Medical Association*. That paper reported on the Stroke Treatment with Ancrod Trial (STAT), conducted at 48 medical sites. The authors concluded that ancrod compared to placebo significantly increased participating patients' functional status at three months.

However a similar European trial, called ESTAT, was stopped because ancrod increased intracranial hemorrhage. Patients in that study received ancrod for 72 hours, and the drug produced an unacceptable rate of bleeding.

"Seventy-two hours is a long time, and they were given the drug in much higher doses," says Kiva Schindler, RN, CCRC, research site director for Marshall L. Nash, MD, at DeKalb Medical Center in Decatur, Ga. "If someone has a big ischemic stroke and you give them a blood thinner for three days, you are going to possibly cause them to bleed into that big stroke."

Neurobiological Technologies cited the higher dosing levels and protocol criteria that permitted enrollment of patients at higher risk of hemorrhage as contributing to the trial's failure.

Patients participating in the two current international, phase 3 trials receive a single individualized intravenous dose, infused over two to three hours. The double-blinded, placebo-controlled trials aim to determine whether infusing ancrod within six hours of symptom onset improves functional outcome at three months. The studies began accepting patients in 2005. Each trial will enroll 650 stroke victims. The company anticipates study participant accrual to continue into 2008 and hopes the lower dose will improve safety.

Potential participants

Study candidates include patients presenting at a participating hospital with symptoms of an acute, ischemic stroke. They must score between a five and 25 on the National Institutes of Health Stroke Scale. The NIH Stroke Scale is a tool used to consistently identify and assess neurological deficits in stroke patients. Completing the scale at different times allows clinicians to assess condition changes over time.

The first symptoms must have begun within six hours of treatment with ancrod. If the person wakes up with symptoms, the last time they felt normal is considered the time of onset. However, doctors typically will offer patients arriving within three hours of symptom onset tPA, the standard of care.

"Once outside the window and the opportunity for tPA is no longer an option, [ancrod] gives us another option," says Leslie Rogers, RN, director of cardiac services at Manatee Memorial.

Emergency department physicians will order a CT scan. Any evidence of intracranial, extravascular blood rules out study participation. Patients with hypertension (systolic greater than 185 or diastolic greater than 105), a baseline fibrinogen level of less than 100 mg/dL, or thrombocytopenia cannot receive the drug. People with a recent or anticipated use of a thrombolytic agent or surgery also are excluded.

After screening arriving patients, emergency department personnel will notify research staff, who immediately respond. Patients or family members must give informed consent.

"It takes the entire stroke team to make this work," Rogers says. "There's close collaboration between physicians, nurses, pharmacy, and radiology."

Potential risks

Intracranial hemorrhage presents the greatest treatment risk. Methodist tries to keep patients' blood pressure low to decrease the chance of bleeding.

"Blood pressure control is important during the first 24 hours," Bledsoe says. "We let them be hypotensive primarily to perfuse the bad area or penumbra around the core of the stroke."

Nurses from the study typically follow up with patients during their recovery. They monitor the fibrinogen level daily for six days to ensure it remains within a therapeutic range.

At DeKalb, a study nurse stays with the patient during the first 24 hours, which helps secure clean, consistent data. The study nurse draws labs at the exact time specified in the protocol, performs neuro checks, and monitors stroke symptoms, such as impaired motor and cognitive function and limited ability to perform activities of daily living.

"We look for any decline in neurological status, which might alert [us that] the patient may have an intracranial hemorrhage or an extension of the stroke," Leonard says.

None of the 24 participants at DeKalb and Gwinnett Hospital System have experienced any major bleeding events. Study teams follow patients for three months, evaluating changes in motor and cognitive function.

Promising results

Because the current trial is blinded, nurses do not know which patients have received the drug and which were given a placebo. However, nurses have noticed that some patients respond better than expected.

"In some patients, we see dramatic improvement," Schindler says. She wonders if it truly is due to the medication, if there could be a placebo effect, or if the extra nursing care related to the study contributes to the better outcomes.

"Our first patient presented to the hospital with a NIH Stroke Scale score of 11 and her NIH Stroke Scale at discharge was a zero," Fisher says. That patient demonstrated severe left side deficits and high blood pressure. "It was amazing. She's still doing great and very upbeat. She is back to baseline as far as quality of life."

Even if the trial proves ancred improves function, it only opens the window of opportunity for treatment. Patients still must learn to call emergency medical personnel at the first sign of stroke.

"Time is brain," Fisher says. "They should call 9-1-1 and get to the nearest hospital."

How ancred works

Ancred acts as a defibrinogenating agent, rapidly depleting plasma fibrinogen levels. It decreases blood viscosity and secondarily produces a clot lysing action. The agent appears to restore and enhance oxygen flow to the affected area of the brain.

"The snake venom is known to change the characteristics of the blood to break down the clots," explains Christine Fisher, RN, stroke coordinator at Manatee Memorial Hospital in Bradenton, Fla. "It also thins the blood to prevent further clot formation and reduces viscosity, allowing

blood to pass through smaller blood vessels and to reach oxygen deprived tissues more quickly."

Drug manufacturer Neurobiological Technologies Inc. of San Francisco reports that studies indicate ancrod progressively reduces viscosity by 20% to 30% from pretreatment levels. The blood gradually returns to normal levels within about 10 days.

"We're intervening in the clotting cascade by interrupting the fibrinogen turning into fibrin," says Don W. Bledsoe, ANP-C, MSN, a nurse practitioner with the stroke team at the Eddy Scurlock Stroke Center at the Methodist Neurological Institute in Houston.