Lowering body temperature could aid standard stroke treatment

May 17 2007

University of Cincinnati scientists have developed a model that could help physicians combine current clot-busting medication with below-normal body temperatures (hypothermia) to improve the treatment of ischemic stroke patients.

Thought to be first report of the temperature dependence of the standard, FDA-approved stroke medication—an enzyme called tissue plasminogen activator (tPA)—in human clots and plasma, the findings could prove useful in predicting the efficacy of tPA over a wide range of temperatures, the UC researchers say.

The work is reported in the May 2007 issue of *Physics in Medicine and Biology*.

It is already known that lowering a patient's temperature reduces the metabolic activity of ischemic (clot-causing) cells, which in turn reduces cell damage and death.

But, says George Shaw, MD, PhD, who led the UC team, while several research centers are studying the use of hypothermia treatment for both stroke and heart attacks, little is known about how effective tPA is in the lab or the human body at lower temperatures.

Using the Celsius (centigrade) scale, normal human body temperature is 37 degrees. Shaw and his team tested tPA, which like most enzymes is very temperature dependent, to see how well it broke up clots at

temperatures ranging from 30 to 39.5 degrees Celsius.

The researchers used blood samples from ten healthy donors to form 226 small clots, exposed the clots to fresh-frozen human plasma and tPA at various temperatures, then measured how much mass the clots lost.

Shaw says that while he and his colleagues fully expected to find that tPA is less effective at lower temperatures, their study enabled them to develop a model to explain the mechanism of how tPA gets into the clot and subsequently breaks it up.

"Around 33 Celsius is what most folks would consider the target temperature in cooling for therapeutic hypothermia," Shaw explains, "although there have been suggestions that 35 Celsius would be useful as well."

The UC researchers found, however, that at 33 degrees Celsius, clots exposed to tPA lose only 8.8 percent of their mass, compared with 12 percent at 37 degrees Celsius.

"So, very crudely," Shaw says, "if you're administering therapeutic hypothermia and tPA at the same time, you might want a higher tPA dosing, since it is less effective at lower temperatures."

Another consideration, however, Shaw explains, is the role of the body enzyme plasminogen, which tPA converts into plasmin, a so-called proteolytic enzyme that actually does the work of dissolving the clots.

"Without sufficient plasminogen," Shaw says, "more tPA won't help, so I suspect if one wants to use hypothermia and tPA at the same time, something else might be needed to help the tPA work better."

Shaw says the model of the tPA-hypothermia interaction that his team

has developed from the study may be useful in helping researchers predict the efficacy of tPA over a wide range of temperatures.

"Knowing the effectiveness of tPA at various temperatures could allow a physician to adjust tPA dosing in a stroke patient if hypothermia is being induced as well," says Shaw.

"There are multiple medications and treatments for heart attacks, but not for stroke," he adds, "because stroke therapies are still in their infancy. This study offers another potential option for treatment."

Source: University of Cincinnati