Significance of Experimental Infarct Size as an Indicator of Therapeutic Efficacy in Humans

To the Editor:

We would like to make a comment not in particular to the article by Shimamura et al but to the use of infarct size in animal experiments as a guide to human cerebrovascular research. Many human studies of treatments with neuroprotective agents for acute ischemic stroke, which had good experimental potential, had disappointing clinical results. This failure can be attributed to many factors. One of the main problems is that reliance on infarct size measurement alone in animals can be misleading as an indicator of therapeutic efficacy in humans. In other words, a multicenter, randomized, placebo-controlled study of inducible NOS inhibitors have provided significant neuroprotection in experimental animals subjected to focal ischemia. Tirilazad mesylate is a potent inhibitor of lipid peroxidation caused by suppression of inducible NOS. Most studies have shown a significant reduction of infarct volume in focal ischemia models. On the other hand, a multicenter, randomized, placebo-controlled study of tirilazad in patients with acute ischemic stroke was halted prematurely because of a lack of benefit. There was in reality a trend toward a worse clinical outcome. A possible explanation for the result is that NO participates in DNA repair.

Moreover, some compounds (eg, basic fibroblast growth factor, osteogenic protein-1) have been associated with functional improvement without affecting infarct size in animals. It is also obvious that histological end points cannot tell whether surviving neurons are functional or dysfunctional or will go on to die in a delayed fashion, and they are less predictive of long-term histology than early behavioral assessments.

We would like to add an alternative hypothesis in the problem of experimental infarct size and its clinical implications. Many studies are based on the supposition that proinflammatory agents are detrimental for the brain and that their elevated appearance after ischemia must be somehow diminished. The offered proof is the increased infarct size, which they usually produce in experimental animals. On the other hand, we can suppose that these agents just help confine and finally clear the damaged brain area. In such a case, the infarct size would be increased, but the chances for the rest of the brain would be conceivably better. Increased intracranial pressure could make the problem more complex, but the main idea remains: it is easier to suppose that what the human body does should be supported rather than to think that it should be reversed.

Let us take the example of tumor necrosis factor-α (TNF-α). Its action in ischemia is described as both detrimental and neuroprotective, depending on the experimental conditions. Elevated serum level of TNF-α is observed after severe head injury and trauma. Intraventricular injection of TNF-α one day before middle cerebral artery occlusion exacerbates tissue injury and is reversed by anti–TNF-α. On the other hand, transgenic animals lacking TNF-α receptors develop significantly larger damage to neurons if focal cerebral ischemia or epileptic seizures. TNF-α pretreatment of cultured endothelial cells, astrocytes or neurons protects them to the same degree as hypoxic preconditioning. Importantly, if necrosis is attenuated by therapy (ie, by reperfusion or antiexcitotoxic agents), then apoptosis may be unmasked or even promoted.

These experimental data can be considered consistent under our hypothesis. Therefore, assessment of therapeutic efficacy in preclinical studies should require, in addition to infarct size, demonstration of benefit on functional measures of motor, sensory, or cognitive deficits. Examples include tests of limb placing, beam walking, grid walking, Rotorod performance, grip strength, balance beam–inclined plane performance, prehensile traction, and cognition (eg, Morris water maze, radial maze, 1-trial passive avoidance, T-maze retention test).

Our conclusion is that experimental infarct size cannot serve by itself as a prognostic indicator in human studies, especially when pro- or antiinflammatory agents are tried.

Disclosures

None.

Nikolaos Sakellariadis, MD
Demetrius Panagopoulos, MD
KAT National Hospital
New Psychiko, Greece


Significance of Experimental Infarct Size as an Indicator of Therapeutic Efficacy in Humans
Nikolaos Sakellaridis and Demetrius Panagopoulos

Stroke. published online August 2, 2007;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2007/08/02/STROKEAHA.107.481853.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/