Acetaminophen for Temperature Reduction in Acute Stroke: Potential but Unproven Benefits

To the Editor:

We read with interest the review by Hemmen and Lyden on induced hypothermia for acute ischemic stroke.1 The review focuses on physical cooling methods in acute stroke. Some points, however, deserve in our opinion a more extensive discussion.

The authors state that controlling body temperature below 36.5°C has been proven to correlate with good clinical outcome. They do not cite controlled clinical trials to support their point, but refer to 2 observational studies instead.

Indeed, well-designed studies have shown a consistent relationship between increased body temperature measured within 12 to 24 hours after onset of stroke, and outcome, but not beyond that interval.2 These studies suggest that reductions in body temperature of 0.5°C might lead to a relative risk reduction in poor outcome of 10%. Reductions in body temperature of this magnitude have been proven feasible in 2 pilot studies of high-dose acetaminophen.3,4

In our view, the uncontrolled studies and small randomized trials in acute ischemic stroke that have been conducted so far have not provided sufficient evidence of safety and feasibility of physical cooling methods. We need more randomized phase II studies with several cooling devices. These studies should explore the relationship between intensity of treatment, temperature reduction, and adverse events, such as arterial hypotension, infections, and cardiac arrhythmias. On the other hand, the risk of complications, the high costs of this mode of treatment, and other logistical barriers imply that there is a need for a simple medical intervention that may reduce body temperature to lesser extent, but is cheap and safe.

Although several national and international guidelines recommend the use of acetaminophen in patients with fever after stroke, it is recognized that there is no evidence available of a therapeutic effect.5 Moreover, most patients develop fever after the first 24 hours, and it appears unlikely that late treatment will have an effect on outcome.

Why not treat all patients early with high-dose acetaminophen? The main reason is that this treatment strategy has not yet been proven to improve functional outcome after stroke. In addition, acetaminophen can be dangerous in high doses and cause liver failure. Use of acetaminophen may delay the recognition of pneumonia and urinary tract infections, and thus lead to delayed treatment and poor outcome.

We conclude that a large pragmatic placebo-controlled randomized clinical trial of acetaminophen in acute ischemic stroke is needed. Exactly such a trial is underway in the Netherlands, PAIS: Paracetamol (Acetaminophen) In Stroke. More than 1100 patients have been included in the trial as of January 2007. We expect to be able to present the trial’s results in 2008.

Disclosures

None.

Helen M. den Hertog, MD
Erasmus MC University Medical Center
Rotterdam, The Netherlands

H. Bart van der Worp, MD, PhD
University Medical Center Utrecht, The Netherlands

H. Maarten van Gemert, MD, PhD
Meander Medical Center
Amersfoort, The Netherlands

Diederik W. Dippel, MD, PhD
Erasmus MC University Medical Center
Rotterdam, The Netherlands

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Stroke. 2007;38:e131; originally published online September 13, 2007;
doi: 10.1161/STROKEAHA.107.485508

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/38/11/e131

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