Independent panel finds alteplase beneficial for acute stroke patients

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A review of an earlier study of the use of alteplase has confirmed that the drug, when given according to the study's protocol, reduced disability in patients with acute stroke.

The review was undertaken after a controversy sparked off by an article in the *BMJ* last year (2002;324:723-9). The earlier study was published in the *New England Journal of Medicine* more than seven years ago (1995;333:1581-7).

The *BMJ* article said that the original study was cited as the reason why the American Heart Association had changed its guidelines on the use of alteplase but pointed out that most of the association's experts on stroke had ties to the drug's manufacturer. The article provoked numerous letters, many of which pointed to possible weaknesses in the original study.

The new review was carried out by an independent panel set up by the National Institute of Neurological Diseases and Stroke (NINDS), which conducted the trial. The results of the review were announced at the annual meeting of the Society of Academic Emergency Medicine in Boston last week.

The panel, chaired by W Michael O'Fallon, a professor of biostatistics, said that analyses

confirmed the trial's finding that alteplase, delivered according to its protocol, reduced disability in patients with acute stroke.

The six member international panel, which included three biostatisticians, addressed critics' concerns about baseline differences among the participants in the severity of stroke—differences that, critics argued, could have favoured the trial's treatment arm.

After adjusting the data for a number of variables, including baseline measures of stroke severity, the committee concluded that the treatment effect was confirmed—actually increasing the odds ratio of benefit from 1.7 in the original analysis to 2.1.

Dr Lewis Goldfrank, director of emergency medicine at Bellevue Hospital, New York, and a panel member, said that a "crisis of confidence" made the reanalysis necessary, because "very little tPA [alteplase] has been prescribed for stroke patients" since the publication of the trial.

"This review process was extraordinary," said Dr Goldfrank, adding that to his knowledge this was the first time a major trial conducted by the National Institutes of Health had undergone reanalysis.

Among those welcoming the

findings was Dr William Barsan, chairman of the emergency medicine programme at the University of Michigan, who said the results were "exactly what I expected." Dr Barsan found the committee's conclusions credible, saying, "This study underwent 10 times more scrutiny than any other study."

However, some problems of the trial did limit the strength of the committee's findings. The panellists identified problems with blood pressure measurements before and after randomisation and with management, including "insufficiently standardized interpretation and implementation of protocol specifications" and "incomplete documentation." They found the deficiencies serious enough to "preclude the use of the study's blood pressure information in either statistical analyses or clinical management." The committee found the deficiencies serious enough that they were unable to use the NINDS blood pressure data in their analyses—analyses aimed at controlling for confounding variables.

"It seems at least a bit strange that they would attempt to reach any firm conclusions about confounding when by their own account they don't have access to what could be critical information," said Dr Jerome Hoffman, professor of emergency medicine at the University of California, Los Angeles.

"I hesitate to comment without seeing their data, no less their methods. Nevertheless, if this was intended to address the question of possible confounding, it is unfortunate that they did not present results for the critical 91-180 minute group, where the NINDS authors themselves have suggested major differences between treatment groups in baseline stroke severity."

Dr Hoffman was the only member of the nine person panel that drew up the American Heart Association's guidelines on stroke who dissented from the view that alteplase should be a recommended intervention for stroke.

Dr David Schrager, professor of emergency medicine at the University of California, Los Angeles, expressed concern about the panel's limited description of its methods and assumptions: "It's a shame that they are sharing their conclu-

ARON HARRIS/AP PHOTO

Kirk Douglas: the United States' most famous stroke sufferer

sions with the world before they are able to share the details of their methods."

Professor O'Fallon has promised that the committee will describe its methods fully in its report, which has not yet been submitted for publication.

"I was never concerned that there was a math mistake in the original analysis," said Dr Schrager. "I was, and still am, concerned that the original and repeat analyses did the right math on the wrong equations—in other words, that the kinds of analyses that they carried out make unreasonable assumptions about the data. After eight long years we have been provided access to the data. We await full disclosure of the methods."

Dr Hoffman is also concerned about over-interpretation of the NINDS data, saying that reliance on a single small study is scientific folly: "Long before there were any questions about baseline differences in NINDS, many of us noted that it remains the only randomised controlled study to show benefit."

A meta-analysis of all the randomised evidence is not considered by experts to be particularly convincing of any benefit to stroke patients from alteplase (*Cochrane Database Systematic Review* 2000;(1):CD000213).

Dr Schrager noted that analyses of patients treated with alteplase for stroke in Cleveland, Ohio, and more recently in Connecticut, showed a tremendous number of protocol violations—and disappointing outcomes. □

Suing doctors who don't prescribe alteplase

Dr Phillip Brewer, assistant professor of emergency medicine at Yale University, is concerned that the committee's findings will lend support to malpractice suits against doctors who do not prescribe alteplase to their stroke patients.

Dr Brewer has provided expert reviews in two such cases. "It is disturbing to me that physicians who have honest reservations about the advisability of using thrombolytics in stroke are being pressured into doing so by a combination of marginal results from one study, active promotion by a drug manufacturer, and the threat of opportunistic litigation by trial lawyers," said Dr Brewer.

Dr Michael Callahan, chief of the Division of Emergency Medicine at the University of California, San Francisco, said that whether giving alteplase for stroke should be a standard of care depends on "the circumstances you are practising under as well as the anticipated published details of this reanalysis." He said, "I'm lucky, I work in the same kind of university environment in which this study was conducted. We have a stroke team and neuroradiologists who can read the CT [computed tomography] scan within minutes. That's very different than many community settings, and if you can't provide those same resources you have to be concerned that you can't provide the same results."