A Pilot Study of a New Thrombolytic Agent for Acute Ischemic Stroke in Taiwan Within A Five-Hour Window

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Background and Purpose—This study was the first clinical trial in Taiwan of a new thrombolytic agent human tissue urokinase type plasminogen activator (HTUPA) in patients with acute ischemic stroke.

Methods—Patients were treated with a single bolus intravenous HTUPA under an open-label dose escalation design within 5 hours after symptom onset. Safety outcomes were assessed by symptomatic and asymptomatic intracerebral hemorrhage (ICH) as well as other bleeding episodes. Preliminary efficacy was measured by National Institutes of Health Stroke Scale (NIHSS).

Results—Three doses of HTUPA (0.3 mg/kg, 0.35 mg/kg, and 0.4 mg/kg) were administered to 33 patients, with the majority of patients (n=29) receiving 0.3 mg/kg. Two cases of fatal ICH occurred: 1 in the patient who received 0.4 mg/kg and the other in the 0.3 mg/kg group. Asymptomatic ICH occurred in 6 patients. Other treatment-related serious adverse events were ecchymosis, hematuria, and upper gastrointestinal bleeding, which were completely recovered. At day 90, in patients treated with 0.3 mg/kg within a 0- to 5-hour window, 34% reached NIHSS scores 0 to 1, whereas of those treated within 0 to 3 hours, 86% reached this score.

Conclusion—Intravenous HTUPA, given at 0.3 mg/kg as a bolus injection within 5 hours after symptom onset, had an acceptable safety and efficacious profile in patients with acute ischemic stroke. (Stroke. 2006;37:918-919.)

Key Words: stroke, ischemic thrombolytic therapy

Stroke is one of the leading causes of death worldwide1-2; in Taiwan, it kills only after cancer and represents the single most common cause of permanent disability.3 Standard treatment in local hospitals has been mostly supportive, whereas tissue plasminogen activator (t-PA) was approved in Taiwan only in 2004. Reports on the use of thrombolytics for stroke patients in the Asian population have been lacking. Human tissue urokinase type plasminogen activator (HTUPA), produced locally, is a genetically engineered hybrid molecule of urokinase and t-PA.4 In canine coronary thrombolytic studies, HTUPA induced prompt and sustained coronary thrombolysis at lower doses when compared with t-PA.5-6 The present study was a pilot analysis of HTUPA in patients with acute ischemic stroke.

Methods
This study was approved by the institutional review board and the Department of Health, Taiwan. Written informed consent was obtained from each participating patient. Patients of cerebral ischemia confirmed by head computed tomography (CT) scans with National Institutes of Health Stroke Scale (NIHSS) ≥9 and ≤20 and who could receive the study medication within 5 hours after the onset of symptoms were eligible to enroll (for brain stem stroke, patients with NIHSS >20 could be included at the investigator’s discretion). Patients with any signs of intracranial hemorrhage or tumor were excluded. Other exclusion criteria followed guidelines from the American Heart Association for the use of t-PA in ischemic stroke patients.7 Head CT scan and neurological evaluation were performed immediately before the administration of HTUPA and at 24 hours and 90 days after treatment. Neurological evaluations with NIHSS, Barthel Index, modified Rankin Scale, and Glasgow Outcome Scale were performed at baseline, 30 minutes (NIHSS only), 60 minutes (NIHSS only), 2 hours, 24 hours, 48 hours, 7 days, 30 days, and 90 days after treatment.

Results
A total of 35 patients were enrolled into the study between June 2001 and July 2004. Among them, 29 received 0.3 mg/kg of HTUPA, 3 received 0.35 mg/kg, and 1 received 0.4 mg/kg. Two patients were withdrawn from the study before administration of HTUPA because of the use of endotracheal and nasopharyngeal tubes with traumatic bleeding.

The mean age of the patients was 69.1±10.9 years; 60% were male. The median NIHSS score was 13 (range 9 to 38). Eighty-three percent of patients had a medical history of hypertension, 43% diabetes mellitus, and 29% hyperlipidemia. Sixty-nine percent of patients had large-vessel athero-
thrombotic stroke and 31% cardioembolic stroke. The mean treatment window was 3.62±0.97 hours, and the mean dose of HTUPA was 20.4±3.8 mg/kg.

The incidence of intracerebral hemorrhage (ICH) within 24 hours after HTUPA administration and its clinical outcomes are shown in the Table. At the lowest dose of 0.3 mg/kg, 1 fatal symptomatic ICH (3%) and 5 asymptomatic ICH (17%) were observed. All these ICH incidences occurred in patients who received treatment in the 3- to 5-hour window; none were in the 0- to 3-hour window. As the dose escalated to 0.4 mg/kg, the first and only patient receiving this dose experienced a fatal ICH, thus enrollment at this dose was halted. In the patients (n=3) who received the next lower dose, 0.35 mg/kg, asymptomatic ICH was observed in 1 patient in the 3- to 5-hour treatment window. After 90 days, this patient showed neurological improvement with NIHSS score changed from baseline score 13 to 5.

Between 24 hours and 90 days, no additional ICH was reported except 1 event of traumatic intracranial hemorrhage in a patient from falling at 1.5 months after administration. Two additional deaths occurred during this study period; 1 was attributable to pneumonia and the other acute myocardial infarction. Other non-central nervous system bleeding events in patients who received treatment in the 3- to 5-hour window; none were in the 0- to 3-hour window. As the dose escalated to 0.4 mg/kg, the first and only patient receiving this dose experienced a fatal ICH, thus enrollment at this dose was halted. In the patients (n=3) who received the next lower dose, 0.35 mg/kg, asymptomatic ICH was observed in 1 patient in the 3- to 5-hour treatment window. After 90 days, this patient showed neurological improvement with NIHSS score changed from baseline score 13 to 5.

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### Discussion

This study was the first clinical trial of a new thrombolytic agent in Taiwanese patients with acute ischemic stroke. When the study began, there were 2 major concerns: 1 being the newness of the test agent HTUPA and the other, the preponderance of intracranial vascular lesion in the Orientals over the Occidental people.9–11 Our study showed that the ICH incidences in Taiwanese patients treated with HTUPA at 0.3 mg/kg with 1 intravenous bolus injection (Table) were within the limits of those reported for t-PA trials performed mostly in Western countries.12–13 However, interpretation of this study is limited because of the small number of patients and the lack of placebos. Further assessment of HTUPA would include using lower dosages, comparison with t-PA in Taiwanese patients, as well as trials of HTUPA in patients of other ethnic origins.

### References

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