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Potential Benefit of Uric Acid for Thrombolytic Therapy in Acute Ischemic Stroke

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Abstract

Alteplase (recombinant tissue plasminogen activator) is the only licensed drug for acute ischemic stroke (AIS) treatment, but only 3–5% of patients with AIS receive thrombolytic treatment using alteplase. Further breakthroughs are needed for thrombolysis in AIS because thrombolytic therapy does not benefit all patients equally. Alteplase administration can induce intracerebral hemorrhage or a low rate of recanalization for occlusion of major cerebral arteries (e.g., internal carotid artery). Recently, the effect of alteplase–uric acid (UA) combination therapy was demonstrated in a clinical trial of AIS patients. UA administration resulted in a significant improvement in functional outcome in patients with hyperglycemia, female patients, and patients who had suffered a moderate stroke. Oxidative stress and antioxidant properties would be differ in each AIS patients after reperfusion. Therefore, the optimal dose of UA may vary according to sex, age, body weight, ethnicity and medical history (e.g., diabetes mellitus). Hence, various study arms may be needed in future, large clinical trials. In the future, if levels of oxidative stress or antioxidant properties can be determined rapidly in AIS patients before treatment, the optimal dose of antioxidant may be ascertained.

Keywords: Uric acid; Thrombolytic therapy; Recombinant tissue plasminogen activator; Alteplase; Acute ischemic stroke

Short Communication

Stroke is a major cause of morbidity and disability. It is predicted that the overall cost of stroke care will account for 6.2% of the total burden of illness in industrialized countries by 2020 [1]. Therefore, a new standard therapy for early critical care in patients with acute stroke that restores their function is needed.

Alteplase (recombinant tissue plasminogen activator) is the only licensed drug for acute ischemic stroke (AIS). Tissue plasminogen activator catalyzes plasminogen to plasmin if alteplase is administered via the intravenous route <4.5 h from the onset of AIS symptoms, which promotes endogenous fibrinolysis and vessel recanalization [2-6]. However, only 3–5% of AIS patients receive thrombolytic treatment using alteplase, mainly due to delays in reaching hospital [7].

The efficacy of alteplase may be limited by its toxicity and by reperfusion injury. Thrombolytic therapy does not benefit all patients equally because alteplase administration can induce intracerebral hemorrhage (ICH) or a low rate of recanalization after occlusion of major cerebral arteries (e.g., internal carotid artery, proximal middle cerebral artery) [5]. Therefore, many patients continue to suffer substantial disability after receiving thrombolytic therapy with alteplase [8]. Thus, new methods to enhance the thrombolytic effect of alteplase and to reduce ICH for AIS patients are needed.

Oxidative stress is a major contributor to brain damage in AIS patients, particularly if ischemia is followed by reperfusion [9]. Co-administration of neuroprotective antioxidants could augment the value of thrombolytic therapy, but neuroprotective antioxidants that are approved worldwide are lacking [3-5,10-17].

Uric acid (UA; $C_5H_4N_4O_3$) is an endogenous product derived from the metabolism of purines. UA is responsible for 60% of the total antioxidant capacity of humans [18]. The antioxidant property of UA includes scavenging of hydroxyl radicals, hydrogen peroxide, and peroxynitrite. UA suppresses the Fenton reaction, chelates transition metals, and prevents lipid peroxidation [19]. The neuroprotective effect of UA has been shown in some experimental models of brain ischemia [20-22]. In a rat model of thromboembolic stroke, co-administration of UA and alteplase elicits synergistic effects compared with administration of these agents alone. Co-administration of UA and alteplase reduces infarct volume, improves neurologic function, and attenuates the inflammatory response [21].

In addition to the synergistic effects seen in models of ischemia, clinical trials have suggested that UA has beneficial effects in AIS treatment. In a clinical trial of AIS patients treated with alteplase, infusion of UA reduced levels of the markers of lipid peroxidation in plasma, such as malondialdehyde [23]. A meta-analysis (10 studies; 8,131 patients) showed that increased levels of UA in serum had protective effects upon neurologic outcomes after AIS, and that high levels of UA in serum at AIS onset were a biomarker of a better prognosis in AIS patients [24]. Moreover, Amaro et al. reported that

higher concentrations of UA are associated with better outcomes after thrombolytic therapy with alteplase [25].

Recently, a double-blind study, "Safety and Efficacy of Uric Acid in Patients with Acute Stroke" (URICO-ICTUS), was conducted in 411 AIS patients treated with alteplase <4.5 h of symptom onset [26]. The study compared administration of UA with that of a placebo [26]. URICO-ICTUS showed that ischemic stroke that worsened upon imaging <72 h occurred significantly more frequently in patients in the placebo group (9%) than in the UA group (3%) (p=0.025) [27]. A tendency toward improvement was observed in functional outcomes at 90 days in the UA group, though the difference was not significant [27]. The addition of UA to thrombolytic therapy resulted in an absolute increase in the prevalence of excellent functional outcome at 90 days of 6% compared with placebo (placebo group, 33%; UA group, 39%; p=0.099) [27]. Neither clinically relevant differences nor significant differences were reported between the two groups with respect to death, symptomatic ICH, or gouty arthritis, thereby showing the safety of UA administration [27].

Acute concentrations of matrix metalloproteinase-9 (MMP-9) in serum have been associated with alteplase administration. Disruption of the blood–brain barrier, hemorrhagic complications, lesion growth, and poor long-term outcome has been noted in alteplase-treated patients [28-33]. UA has been shown to prevent increments in levels of active-MMP-9 in alteplase-treated patients, and this biomarker has been found to be inversely correlated with AIS outcome at 90 days [28,30].

However, the mechanism of action of UA is not known. Reactive oxygen species (ROS) are generated soon after occlusion and reperfusion of vessels [34]. Levels of the markers of oxidative stress are raised before recanalization in patients with AIS undergoing treatment with alteplase [35]. Moreover, alteplase administration induces oxidative stress in rat brains [36], in addition to ROS generation by ischemia and reperfusion. The fibrin-binding affinity of alteplase can be impaired by exposure to ROS, and the characteristic advantage of the thrombus selectivity of alteplase in spontaneous thrombolysis and thrombolytic therapy may be diminished in environments in which ROS are plentiful [37]. Therefore, UA may promote alteplase-mediated thrombolysis through reduction of ROS and of its anti-thrombolytic action.

The clinical evidence and mechanism of action for UA must be clarified. The synergistic effect of UA with alteplase does not benefit all patients equally; thus, a larger confirmatory clinical trial should be planned to establish the benefit of UA with thrombolytic therapy in AIS patients. URICO-ICTUS also showed that UA administration resulted in a significant improvement in functional outcome in patients with hyperglycemia, female patients, and patients who have suffered a moderate stroke [26,30,38]. Patients have individualized oxidative stress and antioxidant properties in ischemia and reperfusion. Therefore, the optimal dose of UA may vary according to sex, age, body weight, ethnicity and medical history (e.g. diabetes mellitus). Hence, various study arms may be required for future large clinical trials.

In the future, if levels of oxidative stress or antioxidant properties can be determined rapidly in AIS patients before treatment, the optimal dose of antioxidant may be ascertained. To ensure combination therapy becomes the treatment of choice for AIS patients, the basic mechanisms of alteplase–UA combination therapy must be determined.

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Conflicts of Interest

Kiyoshi Kikuchi, Salunya Tancharoen, Yoshinaka Murai and Eiichiro Tanaka have no potential conflicts of interest with publication of this review.

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