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Short Communication Open Access

Future Optimal Dosing Regimens for Thrombolysis in Acute Stroke

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Short Commentary

In 2012, stroke was the second most common cause of death worldwide [1]. One in 10 people with stroke die in hospital, and many more suffer ongoing disability, which highlights the need for more effective treatments [2].

Recently, the potential of endovascular therapy for acute ischemic stroke (AIS) using catheter-based devices was reported in five randomized clinical trials (RCTs). In all five RCTs that compared endovascular therapy after intravenous alteplase with intravenous alteplase alone, therapeutic superiority was shown in the former regimen [3-7]. However, standardization of endovascular therapy would exacerbate regional disparities owing due to the lack of endovascular specialists.

Efficacy of intravenous thrombolysis using alteplase (0.9 mg/kg body weight), a recombinant tissue plasminogen activator, has been well established in Western countries since 1996 [8]. Further breakthroughs are needed for thrombolysis in acute stroke because intracerebral hemorrhage (ICH) after alteplase administration and a low prevalence of recanalization of occlusions of a major cerebral artery (e.g., internal carotid, proximal middle cerebral) limit the efficacy of alteplase [9].

In a study that compared 0.6, 0.7, 0.8, and 0.9 mg/kg of alteplase in 1,004 eligible patients, Chao *et al.* reported that 0.9 mg/kg alteplase was not optimal for all patients in an East Asian population [10]. In that study, in elderly patients (71–80 years), mortality and symptomatic intracerebral hemorrhage (SICH) increased with increasing alteplase dose, and a lower dose (0.6 mg/kg) of alteplase was associated with a better outcome [10]. Therefore, the optimal dose of alteplase may vary according to ethnicity and age. Currently, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) is assessing the safety/efficacy of two doses of alteplase (0.6, 0.9 mg/kg) in Australia, Brazil, Chile, China, Colombia, Hong Kong, Italy, Korea, Norway, Singapore, Taiwan, Thailand, the United Kingdom, and Vietnam [11]. ENCHANTED will reveal the optimal dose of alteplase according to ethnicity and age.

In Japan, the efficacy of alteplase (0.6 mg/kg) has been well established since 2005 [9]. The internationally recommended dose of alteplase is 0.9 mg/kg. However, only 0.6 mg/kg is used in Japan, which could result in reduced efficacy [9]. Alteplase–edaravone combination therapy (AECT) has been shown to improve early outcomes in AIS patients compared with those treated with alteplase alone: in 356 pairs in a propensity-matched population, ordinal logistic regression analyses showed that addition of edaravone to alteplase therapy was associated significantly with lower Modified Rankin Scale scores upon hospital discharge [12].

As well as direct evidence from RCTs, circumstantial evidence suggests that edaravone has beneficial effects in AIS. Two large post-marketing surveys have been conducted: the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) and the Japan post-Marketing Alteplase Registration Study (J-MARS). In SITS-MOST, the 0.9 mg/kg dose was evaluated in 6,483 European patients with AIS [13], whereas in J-MARS the 0.6 mg/kg dose was evaluated in 7,492 Japanese patients with AIS [14]. Prevalence of complete recovery at 3 months was identical in the two studies (39%). Interestingly, in J-MARS, edaravone was also administered to 74.6% of 7,492 patients [15], suggesting that combination with edaravone enhanced the effectiveness of the reduced dose of alteplase used in Japanese patients with AIS.

Since its approval for use in Japan in 2001, edaravone (3-methyl-1-phenyl-2- pyrazolin-5-one, Radicut®, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) has entered routine clinical practice [9]. A relatively substantial body of clinical and experimental research has demonstrated that edaravone is a low-specificity antioxidant that scavenges singlet oxygen molecules, the superoxide anion as well as hydroxyl, alkoxyl, alkylperoxyl and methyl free radicals, and exhibits neurovascular protective effects against apoptosis, necrosis, edema and inflammatory cytokines [16-27]. Edaravone is a low-molecular-weight agent with water- and lipid-soluble properties [28,29]. Unlike other free radical-scavengers, edaravone crosses the blood–brain barrier readily, which may explain its therapeutic benefits [28,29]. Furthermore, AECT has been shown to reduce infarct size in a comparison between AECT and alteplase alone in preclinical models [26,27,30]. The fibrin-binding affinity of alteplase can be impaired by exposure to reactive oxygen species (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 [31]. Moreover, edaravone appears to ameliorate alteplase-induced oxidative stress in rat brains [24].

Edaravone is not approved for use in Western countries. The treatment protocol in Japan comprises a twice-daily intravenous infusion administered for ≤14 days. Edaravone has a very short half-life ($T_{1/2}$ = 5.4 min) [32], and free radicals are generated soon after vessel occlusion and reperfusion [33]. Biomarkers of oxidative stress are already raised before recanalization in patients with AIS treated subsequently with alteplase [34]. Recently, Kaste et al. reported that a

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new formulation and dosing regimen of edaravone (high-dose, 3-day continuous infusion) was safe for patients with AIS [35]. It will be interesting to see if that study, conducted in Finland, the Netherlands and the United Kingdom, will influence or accelerate use of edaravone in the European Union.

In a comparison between AECT and alteplase alone in preclinical models, the former ameliorated thrombolysis-related hemorrhage [26,27]. Edaravone attenuated alteplase-mediated matrix metalloproteinase-9 (MMP-9) production, which in turn protected against blood–brain barrier breakdown [26,27]. As well as its effects in preclinical studies, circumstantial evidence suggests that edaravone has beneficial effects in AIS that may be explained by a reduction in the prevalence of adverse events caused by alteplase. Prevalence of SICH development attributed to alteplase infusion is reportedly negatively correlated with the prevalence of combined treatment with edaravone in several RCTs. None of the 6,483 participants in SITS-MOST or the 103 participants in the Japan Alteplase Clinical Trial (J-ACT) received edaravone. However, most participants received edaravone in J-MARS and J-ACT II trials (5,557 of 7,492 participants (74.2%), and 53 of 58 participants (91.4%), respectively) [8]. Prevalence of symptomatic ICH was 8.5% in SITS-MOST, 5.8% in J-ACT, 3.5% in J-MARS, and 0.0% in J-ACT II [8]. Those results suggest that edaravone may inhibit hemorrhagic transformation in patients with AIS who receive thrombolysis with alteplase.

RCTs focusing on dose modification of alteplase, next-generation agents of t-PA (tenecteplase, desmoteplase), endovascular therapy, and sonothrombolysis are ongoing worldwide [9], but AECT should be highlighted. Synergistic effects of AECT are accepted widely, and almost all Japanese patients with AIS receive edaravone. Therefore, it may be difficult for large RCTs that compare alteplase plus edaravone with alteplase alone to be carried out in Japan owing to ethical reasons. AECT requires further investigation in large RCTs in Western countries to ascertain its efficacy unequivocally. Alteplase 0.9 mg/kg plus edaravone (high-dose, 3-day continuous infusion) must be compared with alteplase 0.9 mg/kg in RCTs to show whether such a combination is a breakthrough treatment for AIS. The US Food and Drug Administration has granted edaravone an orphan drug designation for treatment of amyotrophic lateral sclerosis (ALS) [36]. This took place after edaravone was approved as having additional indication for ALS in Japan in 2015 [37]. Therefore, study of AECT in Western countries might also be carried out in the near future. We should remain optimistic about the future of therapeutic intervention for stroke, and continue to explore new strategies to provide optimal care for patients with AIS.

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