Edaravone's Antioxidant Capabilities and its Therapeutic Benefits for Post-Ischemic Stroke: A Mini Review

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Abstract

Acute-ischemic stroke (AIS) is one of the leading causes of death worldwide. IV tPA and thrombectomy have been effective in recanalizing occluded vessels. However, there is often a delay in the thrombolytic effect or completing the thrombectomy. Neuroprotective agents may bridge the gap and slow the conversion of ischemic to infarcted brain. Edaravone is a potent antioxidant capable of sequestering free radicals, reactive oxygen species (ROS) and inhibiting oxidative stress. This mini review highlights edaravone as potential antioxidant, thrombolytic adjunct, and prophylactic for cerebral edema.

Keywords: Edaravone, Tissue plasminogen activator, tPA, cerebral infarction, Amyotrophic lateral sclerosis, ALS, acute-ischemic stroke, AIS, ROS, antioxidants, neurodegenerative diseases, oxidative stress

Introduction

A stroke occurs every 40 seconds with someone dying every four minutes [1]. It is one of the leading causes of death not only in the US but also worldwide [2]. Worldwide, among the patients who survive most remain permanently disabled, thereby compounding the financial impact to society in lost productivity and cost for care [1].

One of the main pathways leading to cell death in ischemic stroke is oxidative stress. Free radical toxicity contributes to an array of cellular damage including inflammation, protein degradation, DNA damage and cellular apoptosis [3]. When combined, these processes all lead to tissue damage and ultimately cell death [3]. Due to a variety of factors, the tolerance to ischemia differs based on collateral circulation pathways, genetic and epigenetic differences [4,5]. Regardless of these individual differences, infractions extend with time ultimately resulting in irreversible injury to a vascular territory.

In attempts to halt the conversion of ischemic to infarcted brain, thrombolytic therapy along with endovascular thrombectomy have been used to lyse the clot or mechanically remove it. However, only

3 percent of patients actually arrive at a time window indicated for the administration of IV tPA (less than 4.5 hours) [6]. Patients with large vessel occlusions with a perfusion pattern indicative of salvageable ischemic brain are now treated with endovascular thrombectomy [7]. With either treatment, and particularly for endovascular treatment, time is required to perform the procedure or if diagnosed at non-thrombectomy capable centre, arrange for transfer to a comprehensive stroke centre [8,9].

Neuronal loss continues until reperfusion is achieved at a rate of 1.9 million each minute, on average [10]. Even once reperfusion is achieved, "reperfusion injury" to ischemic brain may occur [11,12]. Neuroprotective agents may temporize the situation thereby slowing the conversion rate of ischemic to infarcted brain prior to recanalization or to limit reperfusion injury [13-15].

Edaravone, a free radical scavenger improves functional outcomes through free radical scavenging and potentially enhanced thrombolysis when used as an adjunct to IV tPA.16 Since completion of a pivotal trial in 2001, edaravone has been used routinely in Japan to treat patients for acute-ischemic stroke [6,16,17].

Herein, we discuss the mechanisms of action, safety, and efficacy of edaravone in the acute stroke patient populations. We also identify future directions of study for this promising therapy.

Edaravone: A Potent Antioxidant

Ischemic stroke results in oxidative stress and the generation of harmful free radicals and reactive oxygen species (ROS) [3]. These lead to inflammation, tissue damage, and cellular apoptosis by attacking cell membranes and the peroxidation of unsaturated fatty acids into phospholipids [3,18]. The c-Jun N-terminal kinase (JNK) pathway is known to play an influential role in inflammation, cytokine production and cellular apoptosis triggered by oxidative stress [19]. ROS results in the phosphorylation of JNK and leads to multiple death factors [19,20]. Through recent research edaravone is thought to target the JNK pathway and inhibit this "death" pathway

[21]. Edaravone limits free radical and ROS due to its conjugated aromatic system. Furthermore, antioxidants like edaravone have the capability to sequester metal ions to prevent oxidative stress for pre-stroke patients [3]. In many studies the amphiphilic edaravone was found to have a positive correlation with ROS and free radical reduction as well as reduced infarct volume and neurological deficits [3,18,22,23]. Secondary injurious processes (e.g cerebral edema, inflammation) are limited by free-radical and ROS reduction. Secondary to the reduction of ROS, edaravone even has the capability to reduce the production of inflammatory cytokines, cytokine-induced neutrophil chemoattractant, and nitric oxide synthases [3]. Thus, upstream and downstream antioxidant therapy may be a beneficial treatment in altering neuronal damage, limiting edema and recovering the penumbra [3].
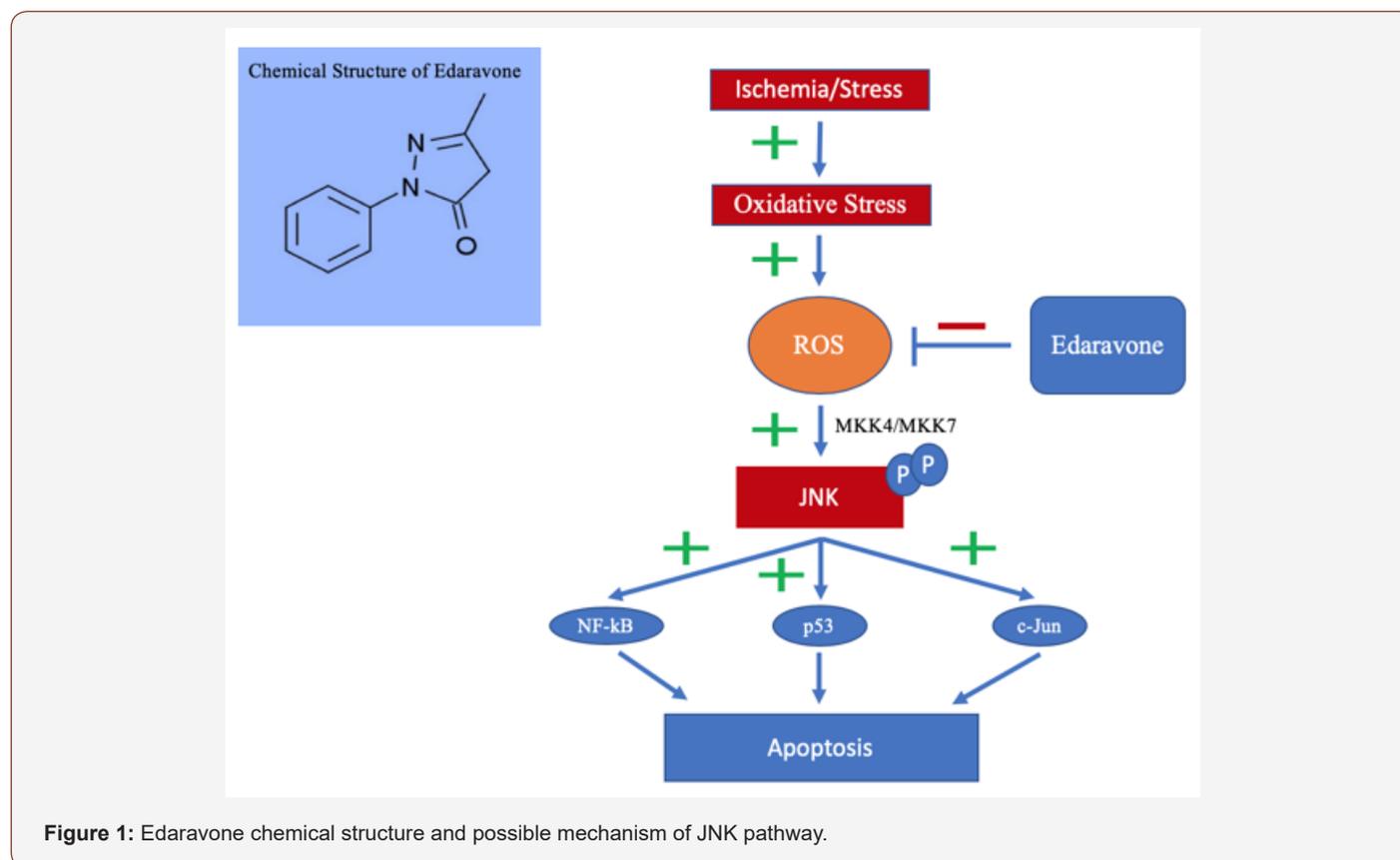

Figure 1: Edaravone chemical structure and possible mechanism of JNK pathway.

Safety

Intracerebral haemorrhage

Ischemic stroke leads to blood brain barrier disruption and may result in intracerebral haemorrhage. The greater the volume of infarcted brain, the more likely haemorrhagic transformation is to occur. While it is obvious IV tPA may increase the likelihood of haemorrhagic transformation due to its direct thrombolytic effect. Recently increased MMP-9 concentrations, linked to haemorrhagic transformation in ischemic stroke, have been linked to IV tPA administration [12,24,25]. Oxidative stress, BBB disruption and mitochondrial mechanisms are all possibly involved in this pathophysiology that lead to haemorrhagic transformation and increased infarct growth [12,24,25]. It is therefore imperative that

neuroprotective agents not increase this risk further.

Edaravone causes an increase vasodilation through the production of prostacyclin's and nitric oxide leading to the theoretical possibility of an even greater increase in ICH [6,17,26,27]. However, when 30 mg edaravone was administered along with IV tPA to patients presenting with M1 or M2 segment of the middle cerebral artery occlusions within 4.5 hours, whether before, during or after IV tPA administration, ICH only occurred in 4 patients (2%) and 2 patients (2%) in the early and late groups, respectively[28]. This difference was not statistically significant, and all the data would suggest that edaravone does not contribute to ICH [28].

Interestingly, in the Enomoto study, it was found that edaravone may potentially reduce the likelihood of ICH [29]. Haemorrhage occurred in 1.4% and 2.7% of the experimental and control groups, respectively [29].

Renal Function

An additional adverse side effect of edaravone administration is renal toxicity [16,30,31]. The renal toxicity is thought to stem from increased blood urea and nitrogen concentrations from edaravone, but the direct mechanism is still unknown [26]. In a study of 207 patients treated with edaravone, 17 patients (8.2%) were able to attribute their renal disorders to edaravone and 190 patients (91.8%) had some other associated factor(s) [30]. Out of these patients, 45 % had reversible renal function after edaravone treatment was stopped [30].

Clinical Efficacy

Functional outcome

Recently there have been multiple clinical trials observing edaravone impact on functional outcome. One of those was a randomized, multi-centre, placebo-controlled trial of edaravone for 250 acute ischemic stroke patients presenting within 72 hours in 16 sites in Japan [32]. An intravenous dosing schedule of 30 mg twice daily was performed for 14 days [32]. The results demonstrated improved neurological outcomes (mRS ≤ 2 within 90 days) after the administration of edaravone within 72 hours of AIS. This study resulted in the widespread adoption of edaravone for the treatment of AIS patients in Japan [32]. The beneficial effects were most pronounced within 24 hours [16].

A small randomized study conducted in India evaluated 50 patients presenting within 6-72 hours of last known well (LKW) [33]. Patients received 30 mg IV edaravone twice daily for 14 days and improved functional outcome was measured by mRS ≤ 2 at 90 days [33]. According to the investigators, a statistically significant difference for functional outcome was observed at 90 days (72%-experimental; n=25 vs 42%-control; n=25) [33].

The most recent clinical trial, the Enomoto trial, conducted in Japan, included the analysis of 11,508 acute ischemic stroke patients undergoing emergent thrombectomy who received either edaravone or a placebo within 24 hours of LWK [29]. Patients received 30 mg IV edaravone once daily for 14 days, and improved functional outcome was measured at 90 days with mRS ≤2. The stroke severity of patients was measured on the Japan Coma Scale (JCS) where at least 47% of the edaravone patients had moderately impaired consciousness upon admission. These results also demonstrated statistically significant improved neurological outcome in 32.3% (n=10,281) and 25.9% (n=1,227) of the experimental and control groups, respectively [29].

Additionally, in a randomized study involving 17 hospitals in Japan with patients presenting within 4.5 hours of occlusions of the M1 or M2 middle cerebral arteries, the timing of edaravone administration whether before, during or after IV tPA was not significant and neurological improvement occurred at all time frames [28]. This study determined that 60 mg edaravone for 14 days was the optimal dosing regimen to improve functional outcome [28, 33,34].

Improved efficacy of thrombolysis

Currently tissue plasminogen activator (tPA) is the only FDA approved drug treatment for one of the leading causes of death globally, acute ischemic stroke. While tPA has been found to be a great thrombolytic agent, a vast majority of people miss the beneficial therapeutic time window of IV tPA [6]. The vasodilatory properties of edaravone was found to increase the efficacy of IV tPA [6,17,26,27,35,36,37]. This effect was apparent in both large and small-vessel occlusions and it did not matter whether edaravone was administered prior/concurrent with tPA or following tPA infusion [17, 28, 38, 39].

Cerebral edema

One of the secondary processes that can cause increased infarct growth and neuronal death is cerebral edema. Cerebral edema leads to increased intracranial pressure which may decrease the cerebral perfusion pressure resulting in further ischemia depending on autoregulation [40]. This cerebral edema can be imaged by diffusion MRI and quantified by the amount of restriction showed [41]. Interestingly, it has been found that edaravone attenuates post-stroke cerebral edema as well through the regulation of aquaporins [16]. Aquaporin-4 and aquaporin-9 were shown in mice to be the major regulators of water homeostasis in the brain and when acted upon by edaravone have led to reduced cerebral edema [40]. This displays edaravone's multi-functional capabilities at combating ischemic stroke through a variety of biological pathways.

Future Directions

In order to establish a true connection of edaravone's effects to post-ischemic stroke, a much larger and more diverse population should be studied. The vast majority of patients studied were Japanese and while these data sets are compelling, it is important to confirm this in a more diverse population. To our knowledge, none of the studies included the effects of edaravone on posterior circulation strokes. This is an important patient population to evaluate where functional outcomes and cerebral edema reduction have the potential to have an even greater impact since the deficits are usually greater in these patients. Perfusion imaging is routinely performed in the triage of acute stroke patients and is used to select the high-risk cohort patients who could benefit from endovascular treatment. Stratification of the efficacy of edaravone by perfusion pattern (no/small, medium, and large penumbra) could refine the cohort benefiting from edaravone as well as its magnitude.

While some of the mechanisms of edaravone's efficacy have been studied in animal models, these mechanisms could be confirmed in humans. Other AIS treatments and combination drug treatments, beyond tPA, have also started to be explored. Borneol, a common anti-inflammatory has been studied through clinical patients with AIS. Borneol is thought to help maintain the blood-brain barrier (BBB) and protect against neurodegenerative processes

[42]. Through 15 studies involving 308 animals, by decreasing the permeability of the BBB, inhibiting inflammation and reducing ROS species, Borneol along with Edaravone helps reduce infarct volume and improve outcome after cerebral infarction [42]. Also through a double blind animal trial it was found Borneol is safe at numerous doses, which makes it a possible drug combination therapy treatment for patients with AIS [43]. "Cocktail" treatments such as this have the potential to synergistically enhance efficacy.

Acknowledgement

Conflicts of Interest

The author has no conflicts of interest regarding this paper.

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