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Mirza Mikayil Aliyev
Azerbaijan State Agrarian University
mirza.aliyev43@mail.ru
Ulduz Yunis Safarova
Azerbaijan State Agrarian University
ulduzsafar@gmail.com
Shafiqa Jahangir Jafarova
Azerbaijan State Agrarian University
shafiqajafarova@gmail.com

CHARACTERISTICS AND THERAPEUTIC EFFECTS OF THE NOVEL FREE RADICAL SCAVENGER – EDARAVONE

Summary

Edaravone is the first free radical scavenger which approved clinically and has an ability to decrease the level of free radicals in cells. Edaravone is a strong antioxidant, which can protect different cells (e.g. endothelial cells) against damage by ROS by inhibiting the lipoxygenase metabolism of arachidonic acid, by trapping hydroxyl radicals, by increasing prostacyclin production, by inhibiting alloxan-induced lipid peroxidation, etc. Because of that, Edaravone is used in treatment of diseases which are associated with oxidative stress.

Key words: *edaravone, free radical, antioxidant, neuroprotective agent, oxidative stress*

Introduction

Edaravone (which is mentioned as EdV in this article), which chemical name is 3-methyl-1-phenyl-2-pyrazolin- 5-one, is the first free radical scavenger clinically approved in Japan. EdV was developed by Mitsubushi –Tokyo Pharmaceuticals.Inc in Osaka, Japan. EdV is being used as a neuroprotective agent since 2001 [1]. The purpose of this work is to show the main features and fields of administration of the novel free radical scavenger.

EdV is a strong antioxidant, which exerts its effects by inhibiting the lipoxygenase metabolism of arachidonic acid, by trapping hydroxyl radicals, by increasing prostacyclin production, by inhibiting alloxan-induced lipid peroxidation, and by quenching active oxygen. These actions provide defense of different cells (e.g. endothelial cells) against damage by ROS. This synthetic antioxidant molecule can quench hydroxyl, peroxyl and superoxide radicals. The antioxidant activity against lipid peroxidative damage induced by water and lipid soluble radicals was shown [2, 3]. Morover, edaravone has been shown to inhibit lipid peroxidation as efficiently as well-known antioxidants such as vitamin C and vitamin E [2]. The lipid peroxidation restraining properties have been proved in vitro [4]. The major and minor products in the reaction of edaravone with peroxynitrite are 4-NO-edaravone and 4-NO2- edaravone, respectively [5].

Table 1. A brief summary of edaravone

Drug name	Edaravone (Radicava®, Radicut)
Molecular formula	C10H10N2O
Molecular weight	174.203 g/mol
Structure:	
Chemical name	1-Phenyl-3-methyl-5-pyrazolone
Company developed	Mitsubishi Tanabe
Approval status	Licensed in Japan and USA
Type	Small molecule

Physical properties	White crystalline powder with a melting point of 129.7°C. Freely soluble in acetic acid, methanol, or ethanol and slightly soluble in water or diethyl ether.
Cellular and molecular targets	Antioxidant. Edaravone is a free radical/ reactive oxygen species (ROS) scavenger, and it reportedly eliminates lipid peroxides and hydroxyl radicals.
Side effects	Urine glucose. Level of glucose in the blood exceeds the ability of the kidneys to absorb it.

The modified form of edaravone is C18-edaravone, which was synthesized by alkylation of edaravone at its allylic position with a C-18 – hydrocarbon chain, and the increased lipophilicity has been determined towards the interaction with liposomes. In the study, it was demonstrated that the newly synthesized molecule has a high affinity for lipid membrane, increasing the efficacy of the unmodified edaravone under stress conditions [6].

Edaravone has low molecular weight which is equal to MW= 174.2; besides, it is both lipid and water-soluble molecule with good cell-membrane permeability [2].

Edaravone's pharma kinetical features in human are following: when administered intravenous (IV) for 40 mg in healthy male adults, it was found that edaravone has half time equal to 0.15-0.17 hours (α phase), 0.81-1.45 hours (β – phase), and 4.5- 5.16 hours (γ –phase). The concentration reached peak at the end of administration and diminished in di-phase and tri-phasic pattern. Edaravone is metabolized by liver and excreted as glucoronated in the urine [7].

The overview of main therapeutic properties of Edaravone

Edaravone's properties make it a promising candidate for treatment of disease associated with oxidative stress [6]. Edaravone is often used to treat acute ischemic stroke, amyotrophic lateral sclerosis [8], Parkinson's disease [9], and AD [10].

In nervous system, edaravone acts as a potent scavenger of oxygen radicals [7]. This medicine can eliminate lipid peroxides and hydroxyl radicals which damage endothelial and neuronal cells [11, 12].

Hidefuni et al. and Aoki et al. [12, 13] showed that edaravone inhibits death of motor neurons and glial cells by stimulating the production of prostacyclin and leukotrienes, reducing the level of free radicals. They have shown that edaravone has favorable effects in animals' models of ALS (amyotrophic lateral sclerosis).

Linting et al. [4] in 2019 also reported the antioxidant properties of edaravone in ALS patients. Moreover, Dejesus-Hernandez et al. [14] investigated edaravone effects in clinical trials, which it appears to be promising candidate to slow progression of ALS in patients. However, oxidative stress might be an essential factor in the progression of the disease [15]. Oxidative stress biomarkers (nitro tyrosine, coenzyme Q10, etc.) are higher in the people with ALS than without. 3 –nitro tyrosine which was confirmed in CSF of ALS patients [16]. Edaravone, which is also known as MCI-186, has been shown to inhibit motor neuron death in animal models by reducing oxidative stress [17, 18]. Edaravone might work in a similar way to ameliorate the disease progression of ALS. Clinical studies showed that during the 6-month treatment period of patients with 60 mg of edaravone revised ALS functional rating scale (ALSFR-S) score was significantly less than before the start of edaravone. Besides, the concentration of 3-NT was low in CSF of almost all patients during study, suggesting that edaravone might protect neuronal cells from oxidative stress [19]. Oxidative stress is also increased in patients with sporadic ALS, based on measurement of the redox balance of plasma coenzyme Q10 [20]. Since oxidative damages are indicated in the pathogenesis of ALS, administration of a free radical scavenger medicine seems a rational therapeutic strategy for disease management.

The Study of Midori et al. [21] reported that edaravone also influences on UA (uric acid) level, which is peroxynitrite scavenger. In ALS patients the level of UA is decreased, however, the level of UA was increased after edaravone administration. Although uric acid is a natural scavenger of peroxynitrite, it scavenges peroxynitrite 30 times greater than does UA. Another scientific researches of Santas et al and Tsukada et al [22, 23] suggested that edaravone also reacts with peroxynitrite much faster than UA. Linting et al. in 2019 [4], also showed that Edaravone might slow progression of ALS. This study suggests that edaravone is safe and effective in more patients with advanced ALS.

Edaravone was also used to develop a novel wound healing anti-inflammatory compound which is composed of edaravone (Ed), hyaluronan (HA) and chitosan (Ch). It is called Ch/HA/Ed membrane, and can be applied as wound dressing material [24]. As it known, during the inflammatory stage of wound healing

process, neutrophils and macrophages release high amount of ROS. Because of this fact, enriching the membrane with edaravone can accelerate the healing. Moreover, Naito et al. [24] corroborated the potency of edaravone to improve the lymphangiogenesis and angiogenesis, which edaravone has positive effect on the healing process. In vivo evaluation of Ch/HA/Ed membrane on the skin wound of the dorsum of the rat suggested that there was a prominent development in the initial healing step that led to a general healing of the wound in comparison with control group. Besides, the healing area showed more dense and thick epithelization. Histologically, the area covered with Ch/HA/Ed membrane showed better granulation than the wound without membrane. Moreover, the preservation of moist environmental balance over injury covered with Ch/HA/Ed membrane supported the migration of keratinocytes, fibroblasts, and endothelial cells which are necessary for skin regeneration. These findings revealed the crucial role of edaravone as a supportive medicine to hasten the wound healing process.

In addition to, Linting et al [25] observed that oxidative stress also may lead to ischemia brain damage through such processes as specific gene expression, anoxic depolarization, and excitatory amino acid release. Oxygen radicals were also found in penumbral cortex during MCA occlusion in rats [26, 27]. Oxidative stress is also implicated in apoptosis. It was established that acute neuronal cell death following brain ischemia can also have apoptotic reason [28].

Referring to these facts, edaravone was the first free radical scavenger, which provided clinical evidence for therapeutic on ischemic stroke and has been applied for the clinical field in Japan since June 2001 [29]. Edaravone inhibits both hydroxyl radical generation and iron induced peroxidative injuries and reportedly has protective effect against ischemic damage [30, 18].

Conclusion

All these studies show that edaravone is a very effective medicine in treatment of various diseases associated with oxidative stress. Edaravone is often used to treat acute ischemic stroke, amyotrophic lateral sclerosis, Parkinson’s disease, and AD. Its neuroprotective, antioxidant effects, moreover anti-inflammatory and wound-healing effects reflects its efficacy in treatment of different pathologies. Investigations in the field of revealing further effects of edaravone and its application in different spheres of medicine still continue.

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