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EDARAVONE: A REVIEW ON ANALYTICAL METHOD AND TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Margi Patel*[1], Krutika Patel[1], Khushbu Patel[2] and Dr. C. N. Patel[3]

[1]Department of Pharmaceutical Chemistry and Quality Assurance, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana- 384001, Gujarat, India.

[2]Associate Professor, Department of Pharmaceutical Chemistry and Quality Assurance, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana- 384001, Gujarat, India.

[3]Principal and Professor, Department of Pharmaceutical Chemistry and Quality Assurance, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana- 384001, Gujarat, India.

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***Corresponding Author**
Margi Patel
Department of Pharmaceutical Chemistry and Quality Assurance, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana- 384001, Gujarat, India.

ABSTRACT

Over the last decade, important advances have been made to support the fact that reactive oxygen species (ROS) are generated and play a harmful role during the acute and late stages of cerebral ischemia. Several drugs, such as radical scavengers and antioxidants, have been evaluated in preclinical and clinical studies. Edaravone is a novel antioxidant that is currently used in Japan for the treatment of patients in the acute stage of cerebral infarction. In particular, postischemic inflammation, leading to brain edema and infarction due to neuronal damage and endothelial cell death, can be ameliorated by Edaravone. In addition to these antistroke effects, edaravone has also been shown to prevent oxidative damage to various extracerebral organs. Therefore, in addition to its usefulness in the treatment of stroke, Edaravone is expected to play an integral role in the treatment of many oxidative stress-related diseases. Edaravone is used to treat amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease; a condition in which the nerves that control muscle movement slowly die, causing the muscles to shrink and weaken). Edaravone is in a class of medications called antioxidants.

KEYWORDS: Edaravone, ALS, Antioxidants, Scavenger.

INTRODUCTION

Edaravone is antioxidant and free radical scavenger. Edaravone is low molecular weight anti-oxidant drug. A novel neuroprotective agent for the treatment of Amyotrophic Lateral Sclerosis. Edaravone is used to treat amyotrophic lateral sclerosis(ALS, Lou Gehrig's disease; a condition in which the nerves that control muscle movement slowly die, causing the muscles to shrink and weaken).[1]

Edaravone is used to treat stroke and amyotrophic sclerosis. It is given by intravenous infusion and by mouth. Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger which has been shown to provide neuroprotection against cerebral ischemia the clinical efficacy of Edaravone has been demonstrated in patients with acute brain infarction Recently, several studies also demonstrated the in vivo efficacy of Edaravone in amyotrophic lateral sclerosis, traumatic brain injury. Although the neuroprotective effects of Edaravone on different models of neurotoxicity have been described, to the best of our knowledge, there is no report on the protective effect of Edaravone against induced neurotoxicity up to now. Parenteral formulations are widely used especially when an immediate psychological response is needed in life threatening emergency conditions and for administering those drug that are destroyed by digestive secretions.[2]

History of Edaravone

In 2017, Edaravone was approved by the FDA to treat amyotrophic lateral sclerosis(ALS) in the United States. Researchers first developed the free radical scavenger Edaravone in late 1980s as a treatment for stroke.[3]

27 July, 2007 approved by **CDSCO.**[4]

Mechanism of Action

Edaravone is a free radical scavenger that scavenges and suppresses the generation of hydroxyl radical and peroxynitrite radical. Edaravone is prime contributor to the progressive degeration of motor neurons(Fig.1). This phenomenon is evidenced by increased levels of 3-nitrotyrosine (3-NT) In addition, lipid peroxides, peroxyl nitrite, and hydroxyl radicals.[5]

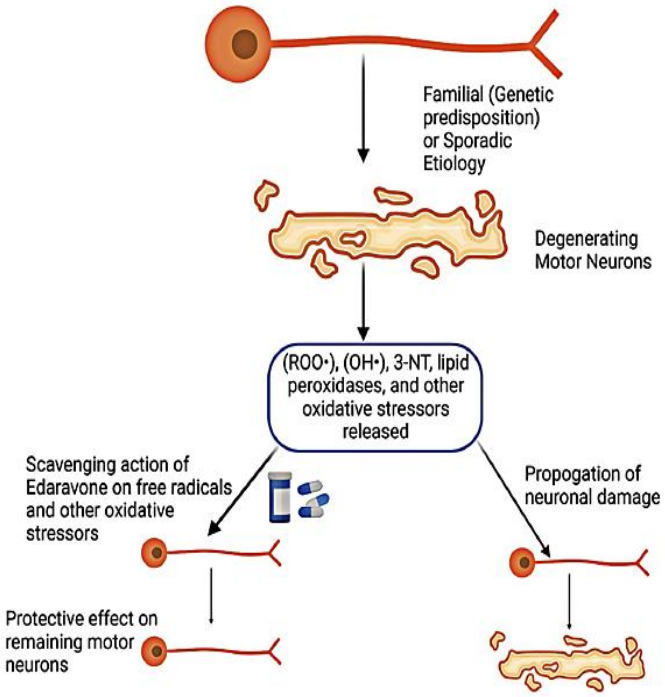

Fig. 1: Mechanism of action of Edaravone.

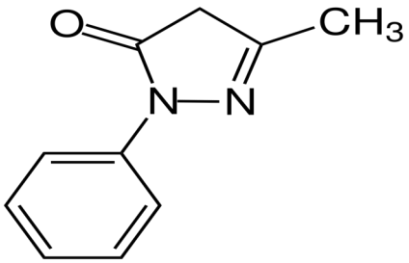

Fig. 2: Structure of Edaravone.

PHARMACOLOGY

Pharmacodynamics

Edaravone is antioxidant and free radical scavenger. Edaravone works to delay the disease progression of neurological disorders such as ischemic stroke and ALS by limiting the extent of neuronal damage or death.[5]

Pharmacokinetics[6]

Absorption

After Oral administration in fasted condition, Edaravone was well absorbed with time reach 0.3 to 0.8 hours. The oral formulation of Edaravone is well absorbed and plasma concentration of unchanged Edaravone increased more than dose proportionally within the dose range of 30 to 300mg.

Distribution

Edaravone has a mean volume of distribution after intravenous administration of 63.1L. The half life of Edaravone is approximately 4.5 to 9 hours.

Metabolism

Edaravone undergoes hepatic and renal metabolism to inactive sulfate and glucuronide conjugates by sulfotransferase and multiple uridine diphosphate glucuronosyltransferase isoforms, and it is excreted mainly in urine as the glucuronide conjugate. Additionally, the PK of edaravone is not affected by age.

Dosing

Edaravone is 60 mg administered via 60-minute IV infusion once daily for 14 days as the initial treatment cycle, followed by a 14-day drug-free period.

Indication

Edaravone is indicated for treatment of amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease; a condition in which the nerves that control muscle movement slowly die, causing the muscles to shrink and weaken). Edaravone is in a class of medications called antioxidant.

Contraindication

Edaravone is contraindicated in patients who are hypertensive to the dynamic substances.

Medical uses

Edaravone is used to treat patients with amyotrophic lateral sclerosis (ALS), which is also known as Lou Gehrig's disease.

Side effects

Irritation, itching, redness of skin, blue lips ,fingernails or skin, change in walking and balance, chest pain, troubled breathing, fast heartbeat, cough, weakness, cracked and dry skin, confusion, irregular, fast or slow breathing.

Use during pregnancy and Lactation

No human data are available regarding Edaravone in duced fetal development risk in pregnant women. At therapeutic doses, Edaravone was associated with development effect, such as increased mortality, decreased growth, delayed sexual development. The excretion of Edaravone in human milk, its effect on the breastfed is unknown.[5]

Geriatric and Pediatric Use

No differences in the safety and efficacy of Edaravone were observed in geriatric patients with ALS compared with the adult population younger than age 65 years. Edaravone has not been evaluated in patients younger than the age of 18 years. However older patients may exhibit greater sensitivity to the drug.[5]

Drug-Drug Interactions

In vitro studies show that therapeutic doses of Edaravone and its metabolites are not inhibited by cytochrome P450 (CYP) enzymes, UGT isoforms, or major transporters in humans. In addition, the active drug and metabolites of Edaravone at clinical doses do not induce CYP1A2, CYP2B6, or CYP3A4.

LITERATURE REVIEW

Literature review of Edaravone

- Edaravone is not official in any pharmacopeia.
- Only non- official reported method are available.

Reported method for assessment of Edaravone

Reported method for Edaravone

Sr. No.	Title	Description	Ref. No.
	HPTLC (High Performance Thin Layer Chromatography)		
1	Development and Validation of HPTLC Method for Determination of Edaravone in Bulk and in Injectable Dosage Form.	**Stationary Phase:** Pre-coated silica gel aluminum plate $60F_{254}$ **Mobile Phase:** Toluene: Methanol (6:4%v/v) **Wavelengh**:254nm.	[7]
2	Development of Stability Indicating **TLC** Densitometry Method of Edaravone Using QbD Approach: Degradation Kinetic Study	**Stationary phase:** Pre-coated silica gel aluminum plate $60F_{254}$ **Mobile phase:** Petroleum ether: Ethyl acetate :Glacial acetic acid (GAA) (6: 4: 0.1 % v/v/v) **Wavelength:** 244 nm.	[8]
RP-HPLC (Reverse phase-High performance Liquid Chromatography) Method			
3	Development and validation of **RP-HPLC method** for estimation of Edaravone in bulk and its injection formulation.	**Stationary phase:** Kromasil column C_{-18} (250 x 4.6 mm, 5 µm) **Mobile phase:** Water: Acetonitrile (55:45 %v/v) **Wavelength:** 243nm **Flow Rate:** 1mL/min	[9]
4	Determination of phenyl hydrazine residue in Edaravone.	**Stationary phase:** Diamonsil C_{18} column **Mobile phase:**	[10]

		Ammonium acetate:Acetonitrile (80:20%v/v) **Wavelength:**233nm.	
5.	Determination of Edaravone and its related substance.	**Stationary phase:** Hypersil C_{18} column **Mobile phase:**1% acetic acid: Methanol (40:60%v/v) **Wavelength:**243nm.	[11]
6	Estimate concentration of Edaravone in human serum.	**Stationary phase:** Hypersil C_{18} column **Mobile phase:** H_3PO_4 buffer (pH-8.2): Methanol (50:50%v/v) **Wavelength:**240nm.	[12]
UV-Spectrophotometric method			
7.	**UV –spectrophotometric** analytical method development for determination of Edaravone in bulk dosage form.	**Wavelength:** 243 nm **Linearity:** 2-14 µg/mL **Solvent:** Methanol	[13]
8.	Development and validation of simple **UV Spectrophotometric** of Edaravone in bulk and injection formulation.	**Wavelength :** 243nm **Linearity:** 1-20 µg/mL **Solvent:** Methanol	[14]
LC-MS/MS Method			
9.	Development and application of a **LC-MS/MS** assay for the simultaneous quantification of Edaravone in beagle plasma	**Stationary phase:** Agilent Zorbax SB-Aq column **Mobile phase:** Water (containing 0.03% formic acid) and methanol (40:60%v/v) **Flow rate :**0.3 mL/min.	[15]
10.	A Novel **LC–MS/MS** Method With an Effective Antioxidant for the Determination of Edaravone, a Free-Radical Scavenger in Dog Plasma and its Application to a Pharmacokinetic Study.	**Stationary phase:** Zorbax Extend C_{18} analytical column **Mobile phase:**0.1% formic acid in water: methanol (90:10%v/v).	[16]

CONCLUSION

The review article carried out an overview about Edaravone. Edaravone is novel neuroprotective agent for the treatment of amyotrophic lateral sclerosis. The pathophysiology of ALS remains poorly understood. Edaravone, a potent pyrazolone free radical scavenger and antioxidant, it was approved for the treatment of ALS and theorized to decrease the effect of oxidative stress in ALS. This review can be used for development of analytical method for estimation of Edaravone in pharmaceutical dosage form in future.

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