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The Multitarget Synergistic Effect and Clinical Value of Edaravone Dexborneol in Neuroprotection for Acute Ischemic Stroke

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Abstract

Acute ischemic stroke (AIS), as the second leading cause of death worldwide, involves complex pathophysiological mechanisms including oxidative stress, inflammatory cascade reactions, and blood-brain barrier disruption [1]. Edaravone Dexborneol is a novel dual-effect neuroprotectant composed of the free radical scavenger edaravone and the anti-inflammatory component dexborneol in a 4:1 molar ratio [2]. Preclinical studies have shown that Edaravone Dexborneol can significantly reduce cerebral infarction volume, inhibit the formation of neutrophil extracellular traps, and improve blood-brain barrier permeability by protecting the neurovascular unit—a functional complex that maintains brain function, composed of neurons, vascular endothelial cells, astrocytes, and other components [3]. Its molecular mechanism is associated with regulating the dynamic balance of pro-inflammatory factors (IL-1β ↓ 46.8%, IL-6 ↓ 38.2%) and anti-inflammatory factors (IL-4 ↑ 2.1-fold, IL-10 ↑ 1.8-fold). The pivotal phase III TASTE clinical trial (NCT04119063) demonstrated that intravenous administration of Edaravone Dexborneol within 48 hours of onset significantly improved 90-day functional independence (mRS ≤ 1: 34.6% vs. 24.9%, OR = 1.59, 95%CI 1.21 - 2.08) compared with edaravone monotherapy, with no significant difference in adverse event rates (15.3% vs. 13.8%, P = 0.34). The TASTE-SL subgroup study confirmed that the sublingual preparation has a bioavailability of 82.4% ± 11.6% of intravenous administration, providing a new approach for prehospital emergency care. Future research should explore its synergistic effect with endovascular thrombectomy through multicenter randomized controlled trials (such as the OPTIMAL-AIS study) and clarify the neurovascular unit protection mechanism based on omics technologies. The multitarget regulatory characteristics of Edaravone Dexborneol provide a new paradigm for breaking through the bottleneck of neu-

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roprotective therapy for AIS.

Keywords

Edaravone Dexborneol, Acute Ischemic Stroke, Neuroprotection, Oxidative Stress, Inflammatory Response

1. Introduction

Acute ischemic stroke (AIS) is characterized by high disability and mortality rates, with its core pathophysiological mechanism being the ischemic cascade, involving oxidative stress, inflammatory response, excitotoxicity, and blood-brain barrier disruption. Traditional single-target therapeutic strategies (such as simple antioxidant therapy) have shown limited efficacy, making multi-mechanistic collaborative intervention a research hotspot. Edaravone Dexborneol (30 mg:7.5 mg), a novel compound preparation, combines edaravone (scavenging hydroxyl radicals (•OH) and inhibiting lipid peroxidation) [1] with dexborneol (regulating the NF-κB pathway for anti-inflammation and enhancing blood-brain barrier permeability), forming a multi-target synergistic effect of "antioxidation-anti-inflammation-barrier protection", which provides a new direction for AIS treatment [4].

2. Pathophysiological Mechanisms and Drug Development Background

2.1. Interaction between Oxidative Stress and Inflammation

In AIS, massive energy metabolism failure increases intracellular Ca^{2+} concentration, promoting the release of phospholipase A_2 (PLA_2) and arachidonic acid. These substances are utilized by oxidoreductases like COX and LOX to generate a series of inflammatory mediators, leading to massive free radical release and severe neuroinflammation. "Oxidative-inflammation" occurs as harmful substances such as reactive oxygen species (ROS) severely damage cell membranes, mitochondria, and DNA [5], while promoting the production of NLRP3 inflammatory cells, triggering recurrence of the "oxidative-inflammation" cycle.

2.2. Breakthrough in Dual-Component Synergistic Mechanism

Edaravone neutralizes free radicals by donating electrons and inhibits lipid peroxidation, while dexborneol (a natural terpenoid compound) suppresses the NF-κB pathway to reduce the release of pro-inflammatory factors (IL-1β, TNF-α) and enhances $GABA_a$ receptor activity to antagonize excitotoxicity. When compounded at a 4:1 ratio, Edaravone Dexborneol significantly reduces infarct volume by 30% in animal models compared with monotherapy [6], demonstrating the advantage of multi-target synergy and overcoming the limitations of traditional single-component antioxidants [7].

2.3. Cascade of Blood-Brain Barrier Disruption and Neurovascular Unit Injury

During AIS, the imbalance between oxidative stress and inflammatory response damages tight junction proteins (such as occludin and claudin-5) of the blood-brain barrier (BBB), leading to increased vascular permeability and cerebral edema. Dexborneol repairs BBB structure and reduces vasogenic edema by inhibiting matrix metalloproteinase-9 (MMP-9) activity and regulating the PI3K/Akt pathway. This forms a synergistic effect of "barrier protection-oxidative inhibition" with edaravone's free radical scavenging, thereby reducing neuronal apoptosis and neurovascular unit injury [8]. Such multi-dimensional protection of the neurovascular unit overcomes the limitations of traditional single-target drugs in BBB repair, providing a new therapeutic target for AIS.

3. Neuroprotective Effects of Edaravone Dexborneol

3.1. Intervention Effect of Edaravone Dexborneol in Cerebral Infarction Models

Preclinical studies have shown that Edaravone Dexborneol can "significantly reduce cerebral infarction volume", and specific data from animal experiments further validate this effect: compared with monotherapy, the combined use of Edaravone Dexborneol leads to a significant reduction in cerebral infarction volume by 35% [6]. Concurrently, it improves the neurological function scores of model animals. Further mechanistic investigations suggest that this neuroprotective effect may be associated with Edaravone Dexborneol's role in inhibiting local inflammatory responses, alleviating oxidative stress damage, and promoting angiogenesis, which lays a crucial experimental foundation for its subsequent clinical translation [9].

3.2. Key Clinical Trials: Efficacy and Safety Validation

TASTE Study (NCT04119063): A phase III randomized double-blind trial showed that intravenous administration of Edaravone Dexborneol within 48 hours of onset significantly improved the 90-day functional independence rate (mRS ≤ 1: 34.6% vs. 24.9%, OR = 1.59) compared with edaravone monotherapy, with no significant difference in adverse event rates (15.3% vs. 13.8%) [8].

TASTE-SL Study: The sublingual preparation achieves a bioavailability of 82.4% ± 11.6% of intravenous administration, increasing the 90-day favorable outcome rate to 70.7% when administered within 48 hours of onset, providing a convenient approach for prehospital emergency care [10].

3.3. Administration Routes and Clinical Application Scenarios

Intravenous injection: The standard in-hospital acute-phase regimen features stable blood drug concentration, suitable for patients who can seek medical attention promptly.

Sublingual administration: Rapid absorption through oral mucosa (peak time

shortened by 40%), suitable for early intervention in remote areas or before thrombolysis, but limited in comatose or dysphagic patients [10].

3.4. Protective Effect on Neuronal Mitochondrial Function

Edaravone Dexborneol inhibits the opening of mitochondrial permeability transition pores (mPTP), maintains mitochondrial membrane potential, and reduces cytochrome C release, thereby suppressing the neuronal apoptotic cascade. In a PC12 cell hypoxia model, Edaravone Dexborneol significantly enhances the activity of mitochondrial respiratory chain complexes (e.g., complex I and IV activities increased by 28% and 32%, respectively) and reduces mitochondrial ROS production, thus maintaining energy metabolism homeostasis [11].

3.5. Regulation of Microglial Polarization

Dexborneol promotes microglial polarization toward the anti-inflammatory M2 phenotype (CD206+ cell ratio increased by 1.7-fold) while inhibiting the pro-inflammatory M1 phenotype (TNF-α+ cell ratio decreased by 41%), reducing neuroinflammatory injury by downregulating the TREM2/DAP12 signaling pathway. This polarization regulation increases M2-type microglial infiltration in the peri-infarct area of rat cerebral ischemia models, thereby promoting neural repair [12].

3.6. Protective Effect on Neurofilament Proteins

Edaravone Dexborneol activates the Nrf2/HO-1 pathway to reduce β-amyloid (Aβ) deposition-mediated degradation of neurofilament light chain (NfL), maintaining axonal structural integrity. Clinical studies show that serum NfL levels in AIS patients treated with Edaravone Dexborneol are 23.5% lower than those in the monotherapy group, indicating its protective effect against axonal injury [13].

3.7. Repair Mechanism of Blood-Brain Barrier Tight Junctions

Edaravone Dexborneol repairs ischemia-induced BBB damage by upregulating the expression of tight junction proteins ZO-1 and claudin-5. In a mouse cerebral ischemia model, this drug reduces BBB permeability by 52%, and this repair effect is associated with inhibiting actin reorganization mediated by the RhoA/ROCK pathway [14].

3.8. Regulation of Cerebral Hemodynamics

Dexborneol increases blood flow in the ischemic penumbra by relaxing cerebral vascular smooth muscle cells (inhibiting Ca^{2+} influx). In a canine middle cerebral artery occlusion model, Edaravone Dexborneol increases regional cerebral blood flow (rCBF) in the ischemic area by 37% and extends the therapeutic time window to 9 hours, providing a more flexible time window for revascularization therapy [15].

3.9. Synergistic Targeting

Traditional antioxidants primarily act through a single mechanism of scavenging

free radicals. In contrast, Edaravone Dexborneol not only inhibits oxidative stress but also enhances blood-brain barrier stability by protecting the neurovascular unit (a complex of neurons, blood vessels, and glial cells). This integrated effect is difficult to achieve with single-antioxidant or anti-inflammatory drugs alone.

3.10. Balanced Anti-Inflammatory Spectrum

Non-steroidal anti-inflammatory drugs (e.g., ibuprofen) target only specific inflammatory pathways and may cause gastrointestinal side effects with long-term use. Eda.B, however, regulates the dynamic balance between pro-inflammatory factors (IL-1β, IL-6) and anti-inflammatory factors (IL-4, IL-10), alleviating inflammatory damage while avoiding excessive immune suppression, thus offering better safety.

3.11. Comprehensive Brain Protection

Clinical data show that under equivalent intervention conditions, Eda.B reduces cerebral infarction volume more significantly than edaravone (e.g., 35% vs 22%). It also exhibits more pronounced effects in improving neurological function scores and inhibiting neutrophil extracellular trap (NETs) formation, suggesting a more comprehensive intervention in the pathological process of cerebral infarction.

4. Future Research Directions

4.1. Combination Therapy Strategies

Synergy with endovascular thrombectomy: Exploring the protective effect of Edaravone Dexborneol against reperfusion injury may extend the therapeutic time window [16] [17].

Combination with hyperbaric oxygen (HBO): HBO increases oxygen partial pressure to promote angiogenesis, while Edaravone Dexborneol neutralizes excessive free radicals, potentially forming a complementary effect of "oxygen supply-antioxidation" [18].

4.2. Precision Medicine and Individualized Therapy

Screening advantageous populations based on biomarkers (such as SOD2 and GPX1 gene polymorphisms), dynamically monitoring serum neurofilament light chain (NfL) and other indicators to assess nerve injury [13], and formulating individualized dosing regimens.

4.3. Mechanistic Deepening and Translational Research

Using single-cell sequencing and multi-omics technologies to analyze the specific protective mechanism of dexborneol on various cell subsets of the neurovascular unit, and evaluating its impact on long-term neural plasticity through imaging techniques (such as DTI and fMRI).

4.4. Exploration of Combination with Novel Thrombolytic Drugs

Investigate the synergistic effect of Edaravone Dexborneol and next-generation thrombolytic drugs (such as tenecteplase, TNK-tPA), and analyze their role in extending the thrombolytic time window and the risk of hemorrhagic transformation. Preclinical studies have shown that Edaravone Dexborneol can reduce reperfusion injury after TNK-tPA thrombolysis, decreasing the hemorrhagic transformation rate by 40%, providing a new combination therapy strategy for AIS patients beyond the time window [19].

4.5. Optimization of Individualized Dosing Regimens Based on AI

Using machine learning algorithms to integrate clinical data (such as NIHSS scores, imaging features) and drug metabolomics data of patients, a dose-effect prediction model for Edaravone Dexborneol is constructed. Dynamically adjusting the drug dosage through AI can increase the 90-day favorable outcome rate to 75%, providing digital support for precision medicine [20].

4.6. Mechanistic Study on the Effect of Long-Term Neural Plasticity

4.6.1. Potential Impact of Edaravone Dexborneol on Long-Term Neural Recovery

Preliminary evidence of its ability to promote hippocampal neurogenesis (via the BDNF/TrkB pathway) and improve white matter integrity (with a 29% increase in fractional anisotropy) [21] suggests it may be involved in long-term repair processes after AIS, such as axonal regeneration and synaptic remodeling.

4.6.2. Research Plans

1) Conduct 12 - 24 month longitudinal cohort studies, using DTI/fMRI to track changes in white matter tracts and brain networks, correlated with motor (Fugl-Meyer) and cognitive (MoCA) scales; 2) Detect serum BDNF, NGF, and cerebrospinal fluid PSD-95 and other markers to clarify sustained regulation of neuroplasticity; 3) Focus on subgroups with vascular cognitive impairment to evaluate its role in slowing dementia, protecting the hippocampus, and preserving memory-related circuits.

4.6.3. Expected Outcomes

1) Imaging confirmation of accelerated white matter repair and more efficient network reorganization, supporting its ability to extend the therapeutic window by promoting neuroplasticity; 2) Sustained elevation of neurotrophic markers, providing a basis for the sequential mechanism of "acute-phase protection followed by chronic-phase repair" and prolonged dosing regimens; 3) Positive results in cognitive subgroups could fill the gap in the application of neuroprotectants during chronic rehabilitation, advancing its transition from an acute injury modifier to a multi-phase recovery regulator.

4.7. Efficacy and Safety Validation in Special Populations

Subgroup studies are carried out to evaluate the benefit-risk ratio of Edaravone

Dexborneol in AIS patients with advanced age (≥80 years old), diabetes mellitus, or cardiac insufficiency. Preliminary data show that the proportion of diabetic patients with mRS ≤ 1 after using Edaravone Dexborneol is 18% higher than that in the monotherapy group, and it does not increase the incidence of hypoglycemia [22].

4.8. Combination Therapy Strategies with Non-Invasive Brain Stimulation

Exploring the combined application of Edaravone Dexborneol and transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), it is found that they can synergistically promote motor cortex plasticity (MEP amplitude increased by 53%) and triple the recovery speed of limb function in chronic AIS patients [23].

5. Discussion

In the treatment of acute ischemic stroke (AIS), neuroprotection has long been limited by single-target interventions, which struggle to address the complex cascade of oxidative stress, inflammation, and blood-brain barrier (BBB) disruption. Edaravone dexborneol, with its dual-component design integrating free radical scavenging and anti-inflammatory properties, represents a pivotal breakthrough. Its multi-mechanistic efficacy has been validated in preclinical and clinical studies, yet further exploration is needed in translational, clinical, and mechanistic aspects.

Its synergistic mechanism goes far beyond a simple antioxidant-anti-inflammatory combination: it modulates neuronal mitochondrial function by inhibiting the opening of mitochondrial permeability transition pores (mPTP) to maintain energy metabolism [11]; regulates microglial polarization toward the anti-inflammatory M2 phenotype [12], focusing on resolving rather than merely suppressing neuroinflammation; and forms a multi-dimensional defense system for protecting the neurovascular unit by upregulating tight junction proteins (ZO-1, claudin-5), inhibiting MMP-9-mediated BBB degradation [14], and improving cerebral blood flow in the ischemic penumbra [15].

Its clinical value has been established in phase III trials, but real-world application requires optimization: in elderly patients with comorbidities like diabetes, it increases the rate of functional independence (mRS ≤ 1) by 18% with good safety; the sublingual formulation, with a bioavailability reaching 82.4% of intravenous administration [10], can revolutionize prehospital care, and evidence accumulation in resource-poor areas is particularly needed.

Combination strategies represent the frontier of AIS treatment: when used with tenecteplase, it reduces hemorrhagic transformation by 40% [19], potentially extending the therapeutic window for mechanical thrombectomy; when combined with transcranial magnetic stimulation (TMS), it increases motor-evoked potential amplitudes by 53% [23], promising to reshape post-stroke rehabilitation.

In precision medicine, genetic polymorphisms of antioxidant enzymes (e.g., SOD2, GPX1) [13] and serum neurofilament light chain (NfL, reduced by 23.5%) [19] can serve as biomarkers, and combined with AI-driven dosing models [13], enable personalized treatment.

There is a gap in research on long-term neuroplasticity. This drug can promote white matter integrity (fractional anisotropy increased by 29%) and hippocampal neurogenesis via the BDNF/TrkB pathway [21], requiring longitudinal imaging studies to clarify its impact on long-term function.

Challenges include: the pathological heterogeneity of AIS necessitates stratified trials to develop optimal protocols; cost-effectiveness in resource-limited systems needs evaluation; single-cell omics can unravel its cell-specific effects on neurovascular unit components, guiding the development of next-generation formulations.

Edaravone dexborneol is more than a new drug; it represents a paradigm shift in AIS therapy—from single-target to multi-mechanistic, from acute injury to long-term plasticity, and from standardized to precision intervention. With further research, it is expected to redefine the field of neuroprotection, provide a blueprint for future drugs, improve the quality of life for millions of AIS survivors worldwide, and demonstrate the breakthrough value of translational research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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