

An overview of clinical and therapeutic implications of citicoline

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Abstract

Citicoline is a complex organic molecule which is essential precursor for the synthesis of a key component of for cell membrane integrity and repair “phosphatidylcholine”. Citicoline has also undergone several toxicological evaluations in multiple animal models and high level of safety has been proven. Citicoline is administered to improve the neurological recovery in various conditions including traumatic brain injuries, stroke, vascular dementia, Parkinson’s disease, and aging. Although results of many studies seems to have beneficial impact of citicoline on several cognitive domains however there is a need for further studies with a greater number of patients to develop uniform criteria and to understand citicoline efficacy for neuroprotection and neural repair.

Key Words : • Citicoline, • Cognitive Function, • Neuro Protection

Introduction

Citicoline (CDP-choline or cytidinediphosphate choline or cytidine 5'-diphosphate choline) is a complex organic molecule that is composed of ribose, pyrophosphate, cytosine and choline that play an important roles in cellular metabolism and participate in the biosynthesis of cell membrane phospholipids. ¹It is an essential precursor molecule for the synthesis of phosphatidylcholine, a key component of for cell membrane integrity and repair. ^{2,3}It has been proposed that the citicoline act to stabilize the cell membranes and reduces the presence of free radicals ⁴ and is administered to improve the neurological recovery in various conditions including traumatic brain injuries, stroke, vascular dementia, Parkinson's disease, and aging. ^{2,3,5}In present article we give a brief overview of citicoline and review the current available therapeutic strategies and possible future advancements.

Pharmacology and mechanism of action

Citicoline is a water-soluble compound which archives greater than 90-percent bioavailability. ⁶ In healthy adults it has been shown that oral dose of citicoline is rapidly absorbed and peak plasma levels are achieved in a biphasic manner (at one hour after ingestion followed by a second larger peak at 24 hours post-dosing). ⁷Citicoline is metabolized by hydrolysis into choline and cytidine in the gut wall and these two products (choline and cytidine) are dispersed throughout the body and enter into systemic circulation for utilization in various biosynthetic pathways, and also cross the blood-brain barrier to re-synthesize into citicoline in the brain. ⁸⁻¹⁰It has also been

evaluated as a neuroprotection and neurofacilitory agent in patients with severe, moderate, and complicated mild TBI. ¹¹Several potential neuroprotective mechanisms of citicoline have been described and reinforcement of intracellular glutathione antioxidative system, attenuation of phospholipase A2 activation and thus prevention of phospholipid degradation, enhancement of phospholipid synthesis, stabilization of cell membranes, restoration of Na⁺/K⁺-ATPase activity and prevention of glutamate mediated neurotoxicity. ^{12,13}

Safety and Dosing

The most effective oral dose for citicoline ranges from 500-2,000 mg/daily. The dose for intravenous and intramuscular route also is same. The safety profile and tolerance of citicoline is excellent and the side effects are rare (never severe) and mainly consist of digestive intolerance, gastrointestinal discomfort and restlessness. ¹⁴⁻¹⁷Citicoline has also undergone several toxicological evaluations in multiple animal models and has been proven to have a high level of safety. ¹Citicoline is synthesized by the body from choline and certain food like liver, meat, beans, eggs, and cruciferous vegetables are good sources of choline.

Therapeutic applications

Post-stroke Rehabilitation

In a number of studies the role of Citicoline has been highlighted and it has been found that it increases the recovery in ischemic ^{18,19} as well as hemorrhagic stroke cases. ²⁰ It has been proposed that phosphatidylcholine synthesis appears to be impaired after cerebral ischemia and citicoline has a role to play in increasing the levels of

phosphatidylcholine by acting on the rate-limiting enzyme.²¹ It has also been suggested citicoline provides neuroprotection in patients with ischemic stroke by decreasing brain levels of glutamate and by increasing the levels of ATP.²²

Learning and Memory

The causes of memory impairment in the elderly include decreased neurotransmitter formation, inadequate circulation (vascular dementia), or Alzheimer's disease.²³ Experimental studies in animals and humans have provided the evidence that Citicoline has ability to promote learning ability and memory functions which are important cognitive processes.²⁴ As citicoline act as an intermediate of phosphatidylcholine biosynthesis, it has been proposed that citicoline may reverse age-dependent histopathological changes within the brain neuronal membrane and can potentially restore memory functions.^{25,26} In a double-blind, crossover trial, it was showed that citicoline improved the ability to recall words and objects.²⁷

Parkinson's disease

Citicoline has neuroprotective and neuronal membrane-stabilizing effects and because of these properties it is expected that citicoline may be beneficial for individuals with Parkinson's disease.²⁸ In addition, citicoline has a levodopa-sparing effect and an ability to increase dopamine synthesis thus it has been concluded that citicoline has the ability to compensate for the reduction of levodopa dosage.²⁹ In the results from one study it was shown there was improvement in speech, gait, posture, tremor, agility, and slowness of movements.³⁰ In another study it was found that the citicoline may increase the efficacy of

levodopa, can help to reduce the dosage requirements for levodopa and overall improvement clinical outcome in patients with Parkinson's disease.³¹

Alzheimer's disease

Citicoline supplementation has been found to attenuate hypoperfusion patterns in blood flow to the brain in elderly individuals with senile dementia.³² Oral administration of citicoline has been shown to improve mental function in patients with early or late-onset Alzheimer's disease (particularly in early-onset Alzheimer's patients).³³ This effect may be due an increased blood flow or Citicoline's cholinergic effects and influence on cytokine production.³³ It is also proposed that citicoline reduces endogenous histamine excesses as excessive histamine levels have been implicated in etiopathogenesis of dementia associated with Alzheimer's disease.³⁴

Traumatic brain injury

Citicoline has been shown to be an effective neuroprotective agent in patients with traumatic brain injury.³⁵ It facilitates memory functions by restoring blood flow to the lesion site.³⁶ Citicoline also showed a trend toward shortening the hospital stay for severe head injury patients while improving motor, cognitive, and mental symptoms.³⁷ Citicolinetherapy has also been shown to be effective to alleviate postconcussional symptoms including improvements in recognition memory, and decreased incidence of headaches, dizziness, and tinnitus.³⁸ It is shown to be safe and well-tolerated in patient populations of all age ranges and with many sub-types of traumatic brain injuries.³⁹

Miscellaneous uses

Citicoline also has been used in many other miscellaneous condition including glaucoma/Amblyopia,^{40,41} ischemic optic neuropathy⁴² with variable results. In experimental spinal cord injury animal studies, citicoline has been found to be as effective as methylprednisolone to enhance recovery.^{43,44}

CONCLUSION

Because of lack of significant adverse effects and has high tolerability of citicoline there has been a growing interest for neuroprotection and neurologic recovery with citicoline. There is enhancing the evidence of the role of citicoline in neuroprotection and neuronal repair. Results of many studies seems to have beneficial impact of citicoline on several cognitive domains however there is a need for further studies with a greater number of patients to develop uniform criteria and to understand citicoline efficacy for neuro protection and neural repair.

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