

Citicholine: Current Role in Ischemic Stroke and Future Perspectives

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Abstract

Stroke is one of the leading causes of morbidity and mortality in the world and in recent years a lot of emphasis has been given to the role of newer drugs in stroke which increase neuroprotection. Citicholine (CDP-Choline; or Cytidine 5'-Diphosphocholine) has been shown to possess efficacy in the management of cognitive impairment in stroke as well as in Alzheimer's disease. It has been demonstrated to be a neuroprotective as well as a neuroregenerative agent in patients of acute stroke. A large number of animal studies and clinical trials exist to support the efficacy of this drug in ischemic stroke and Alzheimer's disease. Few studies have also shown its efficacy in hemorrhagic stroke and Traumatic Brain Injury (TBI). The main effects of citicholine are due to the modification of lipid metabolism in neuronal membranes. It regenerates the levels of phosphatidylcholine in the brain and improves neuronal functions. The drug is relatively safe with a very few side-effects.

Keywords: Citicholine; Ischemic stroke; Neuroprotection

Introduction

Stroke or cerebrovascular accident remains a major health concern worldwide and it is one of the most common causes of physical impairment and disability. It has become one of the commonest causes of Disability Adjusted Life Years (DALYs) worldwide, being second only to Coronary Artery Disease (CAD) [1]. Stroke has been defined as an "acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to involvement of focal areas in the brain" [2]. Stroke may be classified as ischemic or hemorrhagic with ischemic type being the most common.

The goal of rehabilitation in stroke is to improve the functional outcomes of the patients. Neuroprotection has been described as any strategy or combination of strategies that interrupts or slows down the sequence of injurious biochemical and molecular events, which, if left unchecked, eventually result in irreversible injury [3]. In recent years, the role of neuroprotective drugs in improving neurological and cognitive functions in patients of stroke has been greatly emphasized. Various newer drugs for neuroprotection include Piracetam, Edavarone, Citicholine etc.

Citicholine is an organic compound which acts as an intermediate in the synthesis of cell membrane phospholipids. It is better described as CDP-choline or Cytidine 5'-Diphosphocholine. It is basically a nucleotide which plays a pivotal role in cellular metabolism. Its structure comprises of a ribose sugar with a nitrogenous base (Cytosine), Pyrophosphate and Choline [4]. The integrity of central nervous system and the signaling pathways in the brain depend to a great extent on the integrity of neuronal lipids, and thus any derangement in lipid metabolism, as occurs in conditions like stroke, exacerbates neuronal injury [5]. Citicholine, which has effects on phospholipid metabolism in the brain has proven neuroprotective properties [6].

Pharmacokinetics and Drug Metabolism

Citicholine is a water soluble compound which has a bioavailability of around 90% [7]. Oral preparations are rapidly absorbed and plasma concentrations of the drug show biphasic peaks. The first peak is seen at one hour after ingestion followed by a second peak at 24 hours. The drug is metabolized mainly in the gut wall and liver. Its excretion is mainly through respiratory CO₂ and urinary excretion, in two phases corresponding with the biphasic plasma levels. The elimination half life is 56 hours for CO₂ and 71 hours for urinary excretion [8]. The rate limiting enzyme in the metabolism of citicholine is CTP: Phosphocholine Cytidylyl- transferase. Choline and Cytidine are the major metabolites of citicholine hydrolysis [9]. In clinical trials citicholine has been administered via both oral as well as intravenous route.

Mechanisms of Action

Citicholine acts at various metabolic pathways through its metabolites- Choline, methionone, betaine etc. There is strong evidence from animal studies to believe that citicholine acts as a phosphatidylcholine precursor [10]. Citicholine is known to improve cognitive functions in patients of Alzheimer's disease by acting as a precursor of acetylcholine [11]. In patients with neuronal injury, the demand of acetylcholine increases, however, when the choline stores in the brain become low, phospholipids of the brain are catabolized to make choline available and this starts a vicious cycle [7]. Exogenous citicholine supplies the required choline and thus helps protect the integrity of the neuronal membrane. In patients of stroke, two main mechanisms have been postulated for the beneficial effects of citicholine [12]:

Increased synthesis of phosphatidylcholine leading to repair of neuronal membrane.

Reduction of accumulation of free fatty acids at the site of stroke-induced nerve damage.

Apart from regenerating phosphatidylcholine, citicholine also serves as an intermediate compound in sphingomyelin synthesis [13]. Sphingomyelin is an intracellular second messenger in the brain and is formed from ceramide and phosphatidylcholine. Choline has also been shown to restore the levels of cardioplin which is a phospholipid component of the inner mitochondrial membrane [14]. Tumor

Necrosis Factor (TNF) is released during ischemic stroke and this stimulates sphingomyelinase. This process is mediated by Arachidonic Acid pathway [15]. Modulation of phospholipase activity by citicholine results in inhibition of sphingomyelinase and helps improve neuroprotection.

S. No	Year	Authors	Animal Studied	Intervention	Results
1	2002	Adibhatla et al. [5]	Gerbils	Citicholine injected after artificially inducing brain ischemia	Restored phosphatidylcholine levels. Inhibited FFA release
2	2001	Adibhatla et al. [5]	Gerbils	Cerebral ischemia induced in gerbils	Restored levels of phosphatidylcholine, sphingomyelin & Cardioplin Increased glutathione levels and glutathione reductase activity
3	2000	Baskaya et al. [41]	Rats	Citicholine administered intraperitoneally in animal models of cerebral ischemia	Decreased brain edema & breakdown of BBB in brain injury
4	2000	Shuaib et al. [42]	Rats	MCA occluded Citicholine given alone or in combination with Urokinase	Enhanced neuroprotection seen in rats treated with citicholine plus Urokinase
5	1999	Andersen et al. [43]	Sprague-Dawley rats	Embolism created in carotid arteries	Size of cerebral infarction was reduced in Citicholine plus-rTPA group.
6	1998	Bruhwyler et al. [23]	Normal dogs	Dogs put through Operant conditioned- learning experiments for 42 days	Citicholine administered dogs had superior memory processes
7	1996	Schabitz et al. [44]	Rats	Focal ischemia induced by blocking right MCA for 2 hours, then treated with Citicholine in 100 mg/kg and 500 mg/kg doses	Rats treated with higher doses of Citicholine had smaller infarct volumes
8	1996	Aronowski et al. [20]	Rats	Ischemia induced by artificially occluding lateral middle cerebral artery	Delayed behavioral dysfunction
9	1993	Drago et al. [22]	Rats	Citicholine administered intraperitoneally to rats with cognitive and motor impairment	Improved learning and memory capacity judged by using tests of active and passive avoidance behavior
10	1993	Petkov et al. [45]	Rats	Memory deficits induced via oxygen deprivation, electric shock & scopolamine	Improved memory performance in older but not younger rats

Table 1: Summary of Animal Studies on Citicholine

FFA: Free Fatty Acids; BBB: Blood Brain Barrier; MCA: Middle Cerebral Artery

Citicholine has also been demonstrated to decrease the accumulation of β -amyloid, which is accumulated in the brain tissue of patients with

Alzheimer's Disease. β -amyloid is known to play a central role in the pathogenesis of Alzheimer's Disease. However this role has not been very extensively studied in humans, but the animal studies on rats have confirmed these findings [16]. Animal studies have also demonstrated that citicholine increases the levels of neurotransmitters in the brain. A study on rats revealed that citicholine increased the levels of norepinephrine in the cerebral cortex and hypothalamus; dopamine levels increased in the corpus striatum; and serotonin levels

increased in the cerebral cortex, striatum and hypothalamus [17]. This is a potential role being investigated for the use of citicholine in Parkinson's Disease.

In a recent study by Hurtado et al., it has been shown that Sirtuin 1 plays a pivotal role in the neuroprotective actions of citicholine [18]. In this study which was conducted on rats, permanent focal ischemia was induced and the rat brains were removed after 24 and 48 hours of inducing ischemia for Western Blot analysis and infarct volume determination. Treatment with CDP-choline increased SIRT1 protein levels in brain of these rats.

Evidence from Animal Data

In a study on gerbils, artificially induced ischemia was preceded by injection of citicholine into the cerebrum of gerbils. This study revealed restoration of phosphatidylcholine levels and inhibition of fatty acid release, thus suggesting the role of citicholine in stabilization of neuronal membrane [19]. Citicholine has also been shown to delay the cell membrane damage in the brains of rats who were subjected to artificially induced occlusion of lateral middle cerebral artery [20]. In a recent study by Diederich et al., in 2012, it has been shown that apart from neuroprotective effects which have been known for a long time, citicholine also has substantial neuroregenerative potential [21].

Citicholine has also been shown in animal studies to improve memory and learning. In a study on rats, citicholine was injected intraperitoneally to rats who had prior cognitive and motor impairments. Results were interpreted using tests of active and passive avoidance [22]. Citicholine improved learning and memory. It also been shown to improve learning and memory in young, normal dogs [23]. Table 1 summarizes the important animal studies conducted on Citicholine.

Thus, we see that the animal data is sufficient at present to strengthen the ongoing clinical trials on Citicholine. As per the Stroke Academic Industry Roundtable (STAIR) criteria for neuroprotection, any agent may be taken up for clinical trials only if pre-clinical studies have shown a reduction in infarct volume as well as functional benefit of the agent under consideration [24]. As we have seen from Table 1 and the preceding sections that animal studies have clearly documented a reduction in infarct volumes as well as a better performance on functional scores in animals. Hence large scale clinical trials are now warranted.

Evidence from Clinical Data

The efficacy of citicholine has been established through many clinical trials. A meta-analysis of ten trials enrolling 2279 patients suggested that stroke patients who were put on citicholine had reduced frequencies of death and disability [25]. In a study by Nipunjot Grewal et al, in India, way back in 2003, statistically significant improvement

was seen in NIHSS score in ischemic stroke patients on second and third days of admission [26]. In yet another study, effects of citicholine were measured using diffusion weighted MRI [27]. Significant correlations were obtained between lesion volumes on MRI and various clinical parameters in patients receiving citicholine.

Iranmanesh et al studied the efficacy of citicholine in increasing the muscular strength in patients with non-traumatic cerebral hemorrhage [28]. In this double-blind study, conducted on 32 patients, muscular strength improved significantly in patients receiving citicholine injections compared to those on placebo with a p-value of 0.019. This was a significant study, because it showed the effects of citicholine in hemorrhagic stroke. Most previous studies had shown efficacy in ischemic strokes only. Apart from non-traumatic brain injury, the role of citicholine was subsequently studied in patients suffering from Traumatic Brain Injury (TBI), in the Citicholine Brain Injury Treatment (CORBIT) trial [29]. However, the effectiveness of citicholine in TBI could not be established.

The ICTUS trial (International Citicholine Trial on Acute Stroke) has emerged as the single, phase III, multicentric, double-blinded, randomized, placebo-controlled trial for the use of citicholine in acute ischemic stroke [30]. This was a sequential trial in patients with moderate to severe acute ischemic stroke, admitted at University hospitals in Germany, Portugal and Spain. 2298 patients were enrolled in this study from November 2006 to October 2011. The trial was stopped for futility at the third interim analysis on the basis of complete data from 2078 patients. This trial has shown that citicholine is not efficacious in the treatment of moderate to severe acute ischemic stroke.

In a double-blind trial of 84 elderly patients in 1989, citicholine was given to patients with mild to moderate memory loss and the status of the patients was reassessed using the MMSE scale and the Randt Memory Test [31]. Significant improvement was seen in patients who received citicholine. In a recent double-blind, placebo-controlled trial of thirty patients of Alzheimer's disease, a 12-week course of citicholine showed improvement on clinical scales like Alzheimer's Disease Assessment Scale (ADAS) [32]. Table 2 summarises the important clinical trials of Citicholine.

S. No	Year	Authors	Type of Study	Sample Size	Inferences
1	2012	Antoni et al. [30]	Randomised, double-blind, placebo-controlled, multi-centre	2298	Citicholine is not efficacious in the treatment of moderate to severe acute ischemic stroke
2	2001	Clark et al. [46]	Double-blind, multicentre	899	Citicholine is safe but ineffective in improving outcomes in patients of acute ischemic stroke
3	1997	Clark et al. [47]	Multicentre. Double-blind study	259	The Barthel Index and NIH Stroke Scale improved
4	1997	Alvarez et al. [48]	Double-blind, crossover trial	24, memory impaired, elderly patients	Improved the ability to recall
5	1989	Agnoli et al. [31]	Double-blind trial	84	Improvement in global memory efficiency and cognitive function

6	1988	Tazaki et al. [49]	Multicentre, double-blind, placebo-controlled	272	Promoted recovery from reversible tissue damage in acute stages of stroke.
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Table 2: Summary of Important Clinical Trials on Citicholine

Safety Profile and Adverse Drug Reactions

Citicholine is a relatively safe drug with very few adverse drug reactions having been reported. Its LD50 is 4600 mg/kg in mice [33]. No significant toxic effects were observed in a 30-day study of the toxicity of the drug in two groups of rats. No deleterious effects were seen in blood chemistry, organ histology or urinary parameters [34]. It shows a low toxicity profile in humans as well. In a short-term, placebo-controlled, cross-over study in healthy adults, the only side effect shown was transient headache. No changes were seen in hematological, biochemical or neurological parameters [35]. A large drug surveillance study analysed the result of citicholine treatment in 2817 patients. A total of 151 incidents of side-effects were reported which reflected only 5% of the sample size. Transient stomachache and diarrhea were the commonest side effects, seen in 102 patients. Hypotension, tachycardia and bradycardia were reported in 16 cases only [36].

Other Potential Therapeutic Uses

Alzheimer's disease

Apart from ischemic stroke and to some extent, hemorrhagic stroke, the efficacy of citicholine has been demonstrated in animal studies as well as in clinical trials in cognitive improvement in Alzheimer's disease [32]. Further studies however are required to furnish more evidence regarding the same.

Vascular dementia

The efficacy of citicholine in vascular dementia has been studied in small clinical trials. In a double-blind trial, involving 30 patients of vascular dementia diagnosed on the basis of MRI as well as on the basis of neuropsychological testing, no significant difference was found between treatment and placebo groups [37]. Therefore, more extensive and elaborative studies have to be conducted to study this effect of citicholine.

Parkinson's disease

Citicholine has been shown in animal studies to improve dopamine secretion [17]. Based on this hypothesis, a double-blind, placebo-controlled, cross-over trial was conducted on patients with Parkinson's disease. There was improvement in bradykinesia and rigidity with citicholine, however tremors remained unchanged [38].

Glaucoma

Clinical trials have suggested that citicholine repairs the damage to optic nerve which occurs in glaucoma [39]. It provides neuroprotection to retina by enhancing phosphatidylcholine synthesis. It is postulated that dopaminergic stimulation is the major mechanism for the effect of citicholine on the retina [39]. In a double-blind, placebo-controlled trial using citicholine, retinal and visual functions were improved in patients of open angle glaucoma [40].

Conclusion

Citicholine is a choline donor and an intermediate compound in the biosynthesis of phospholipids and acetylcholine. It improves the integrity of neuronal membranes and reduces ischemic injury in the brain. Various clinical trials have established the effectiveness of this compound in acute stroke. It has also been shown to improve cognitive functions in patients of Alzheimer's disease and vascular dementia. It is a relatively safe drug with no serious side-effects. Although the pre-clinical studies have suggested a very strong role of Citicholine in acute ischemic stroke, however, the clinical trials have generated conflicting results, with the largest trial (ICTUS trial) showing no efficacy in stroke. However all clinical trials have confirmed that it is a safe drug. Therefore, the use of this drug in clinical practice is still not recommended and more clinical trials with larger sample size may be needed to confirm the current status of the drug in clinical use.

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