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Review Article

Pharmacological Action and Clinical Use of the Drug Ceraxon (Citicoline): A Review of Experimental Data and Clinical Studies

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Abstract

Cytidine 5-diphosphocholine (CDP-choline, or citicoline) is an indispensable intermediate in the biosynthesis of structural phospholipids in cell membranes, in particular phosphatidylcholine. The review is dedicated to the study of citicoline (Ceraxon). The experimental data on its effect on traumatic injury and experimental cerebral edema, as well as the results of clinical use in traumatic brain injury and its consequences, are highlighted.

Keywords: *Citicoline; Acetylcholine; Traumatic Brain Injury; Cerebral Edema; Post-Traumatic Memory Impairment*

Introduction

Citicoline is the generic name of the pharmaceutical substance that is cytidine-5'-diphosphocholine (CDP-choline), which is identical to the natural intracellular precursor of phospholipid phosphatidylcholine [1]. In the Central nervous system (CNS), structural phospholipids of the neuronal membrane are necessary for proper maturation of the brain [2-4], including astrocytes [5]. It is believed that phosphatidylcholine is important for the growth of neuronal processes and the regeneration of nerve cells [6]. Phospholipids are an essential component of cell membranes and are characterized by a high rate of metabolism and renewal, which requires continuous synthesis of these substances to ensure proper functioning of cell membranes and, therefore, cells [7-9]. Cell membranes damage and phospholipid metabolism disorder play an important role in the pathophysiology of cerebral edema and traumatic brain injury [11-14].

CDP-choline is a mononucleotide which consists of ribose, cytosine, pyrophosphate, and choline whose chemical structure corresponds to 2-oxy-4-aminopyrimidine [15]. CDP-choline is an essential intercellular substance for the synthesis of structural phospholipids of cell membranes, and the formation of this substance from phosphorylcholine is a rate-limiting reaction in this biochemical process [16]. CDP-choline is also connected to acetylcholine metabolism. Thus, exogenous CDP-choline serves as an exogenous source of choline and cytidine. Choline is involved in several neurochemical processes. It is a precursor and metabolite of acetylcholine, plays a role in single-carbon metabolism and is an essential component of different cell membrane phospholipids [17]. The cytidine fraction, once transformed in uridine, is used for DNA and RNA synthesis as well as for the synthesis of membrane constituents and glycosylation, having also an important effect on purinergic receptors [18].

Experimental studies of citicoline effects

A sufficient amount of experimental data on the effects of citicoline on traumatic brain injuries and brain edema have been accumulated. Ogashiwa., *et al*. [18], in an experimental model of head injury in monkeys, established a significant dose-effect relationship between

citicoline dose and coma duration, that started to be significant at doses of 60 mg/kg ($p < 0.05$). Watanabe., *et al*. [19], studying the effects of several activators of brain metabolism, have found that citicoline increased glucose incorporation and metabolism and decreased lactate accumulation in the brain, and also induced a slight increase of cerebral blood flow.

M Alberghina., *et al*. [11], in a study on nerve tissue response to a contusion lesion, showed that a moderate increase occurred in the activity of choline phosphotransferase and was associated to a greater increase in the activity of phospholipases A2 and several lysosomal hydrolases. They also found an increased number and size of lysosomes during neuronal regeneration. E Arrigoni., *et al*. [20] have shown citicoline to be able to completely inhibit activation of phospholipases A2 without altering choline phosphotransferase activity. L Freysz., *et al*. [21] showed that, in addition to decreasing phospholipase A1 and A2 activity, citicoline decreases free fatty acid release under hypoxic conditions, thus adding its activating capacity of phospholipid reconstruction, which is consistent with the conclusions of several other authors. DR Algate., *et al*. [22] studied the effects of citicoline in an experimental model of epidural compression in anesthetized cats. The authors noted that animals treated with citicoline had a greater resistance to the effects of mechanic brain compression as compared to animals in the control group. They also found that respiratory and cardiovascular changes were less intense in treated animals and concluded that citicoline provides a significant protection against the lethality of epidural compression. These results are consistent with those obtained of O Hayaishi [23] and Y Kondo [24], which showed an improvement in the electroencephalography tracing following administration of citicoline to cats undergoing experimental brain compression, and also in animal survival quality.

F Boismare [11,25] studied the effect of citicoline therapy on catecholamine levels in an experimental model of craniocervical trauma without direct blow (whiplash injury) and found increased dopamine levels and decreased norepinephrine levels in the brain following trauma. This type of lesion causes postural dysregulation of brain supply as well as behavioural and learning disorders, that are related to accelerated degradation of cerebral norepinephrine. In animals treated with citicoline, trauma did not change the levels of these amines. The author emphasized the protective role of citicoline, due to its stabilizing effect of catecholamine exposure in brain.

CE Dixon., *et al*. [26] analyzed the effects of exogenous administration of citicoline on motor deficits, spatial memory capacity, and acetylcholine levels in dorsal hippocampus and neocortex in a model of TBI in rats, induced by a controlled lateral impact. Citicoline was administered intraperitoneally at a dose of 100 mg/kg for 18 days from the first day following the injury. Saline solution was administered to another group of animals. Motor assessment was performed with the help of balance test for which animals had previously been trained, and cognitive assessment was made with a variant of the Morris maze test, which is sensitive to cholinergic function. Microdialysis methods were also used to analyze the effects upon acetylcholine release. On day 1 after the lesion, citicoline-treated animals showed a significantly longer balance period as compared to animals receiving saline solution (39.66 ± 3.2 secs. versus 30.26 ± 2.9 secs.; $p < 0.01$). In addition, animals treated with citicoline developed significantly less cognitive deficits. Using microdialysis methods, after a single administration of citicoline by the intraperitoneal route, a rapid increase in acetylcholine production was observed as compared to baseline, that was maintained for up to 3 hours, in both dorsal hippocampus ($p < 0.014$) and neocortex ($p < 0.036$), while no changes were noted in animals receiving saline solution. Authors concluded that posttraumatic deficits in spatial memory function are due, at least partially, to deficiency changes in cholinergic transmission, that are weakened with citicoline administration.

MK Baskaya., *et al*. [27] using a rat model of traumatic brain injury examined the effects of citicoline upon cerebral edema and rupture of the blood-brain barrier (BBB). Following experimental TBI animals received citicoline (50, 100, 400 mg/kg) or saline solution intraperitoneally. TBI caused an increase in water content percentage in brain parenchyma and Evans blue extravasation (a marker of BBB rupture) at the damaged cortex and ipsilateral hippocampus. The 50 mg/kg dose of citicoline was not effective, while at 100 mg/kg dose a reduction was seen in Evans blue extravasation in both regions, although this dose decreased cerebral edema only in the damaged cortex. The 400 mg/kg dose of citicoline significantly reduced cerebral edema and the BBB rupture in both regions. Authors concluded that these results suggest citicoline to be an effective neuroprotective agent upon secondary changes occurring in association to TBI.

Along with this, the effects of citicoline in spinal cord injuries was studied. It was shown that intraperitoneal administration of citicoline 300 mg/kg 5 minutes after injury significantly reduced lipid peroxidation and improved motor function in treated animals [28]. After a systematic review of the literature on animal models, L Wang., *et al*. [29] concluded that citicoline is one of the most effective adjuvant treatments combined with surgery in peripheral nerve laceration.

In the experimental studies mentioned above, it was shown that citicoline administration led to a significant reduction of brain edema, improvements in EEG tracing and impairment of consciousness, as well as increase in survival quality. The effect on the level of consciousness is explained by facilitating action of the central nervous system induced by stimulation of the ascending reticular activating system of the brain stem. Based on these experimental assumptions, many clinical trials have been conducted to determine if these effects can be used in the treatment of patients with TBI.

The use of cytocholine for traumatic brain injury

HS Levin [30] conducted a study in 14 patients with post-concessional syndrome after a mild to moderate head injury. This syndrome is characterised by symptoms such as headache, dizziness, memory and sleep disorders. In this study, patients treated with citicoline for one month experienced improvements in memory performance, particularly in recognition tests, that were statistically significant compared to the placebo group. However, in a simple-blind study in patients with mild TBI [31], the authors were unable to demonstrate differences between citicoline and control with regard to the evolution of post-concussional symptoms. Despite this fact, CDP-choline is considered as one of the agent for the treatment of post-concussion syndrome.

In a series of studies conducted by J Leon-Carrion., *et al.* [32-34], the effects of citicoline in posttraumatic memory disorders were studied. In a group of 7 patients with severe memory deficits, the authors measured the effects of administering 1g citicoline on cerebral blood flow, as measured by the 133Xe inhalation radionuclide technique. Two tests were made, one at baseline and the other 48 hours later, under the same conditions, except that patients had taken the drug one hour before the test. All patients showed a significant hypoperfusion in the inferoposterior area of the left temporal lobe at the first measurement, which disappeared after citicoline administration. In the second study, 10 patients with severe memory deficits were randomized into two groups with a short-term memory rehabilitation program. One group received 1 g/day citicoline orally for the 3 months that the neuropsychological treatment program lasted, whereas the other group took a placebo. Neuropsychological rehabilitation combined with citicoline resulted in improvements in all evaluated areas of memory and reached statistical significance in verbal fluency and the word learning Luria test. CDP-choline is considered as an agent for the treatment of post-traumatic cognitive disorders [35], which also improves survival quality [36].

A Cochrane review of citicoline for the treatment of head injury has been published [37]. In 2012, the results of the COBRIT (Citicoline Brain Injury Treatment Trial) trials were published [38,39], clinical trial identifier: NCT00545662. The COBRIT trial was a double-blind, randomized phase 3 study that was conducted between July 20, 2007 and February 4, 2011, among 1213 patients. Its goal was to determine effects of citicoline on the functional and cognitive outcome in patients with complicated mild, moderate and severe TBI. Patients were randomized to be treated with citicoline at a dose of 2000 mg orally once a day or placebo for 90 days. The main outcomes were functional and cognitive status, assessed at 90 days using the TBI-Clinical Trials Network Core Battery. A global statistical test was used to analyze the 9 scales of the core battery. Secondary outcomes were functional and cognitive improvement, assessed at 30, 90 and 180 days, and assessment of the long-term maintenance of treatment effects. Rates of favorable improvement for the Extended Glasgow Outcome Scale were 35.4% in the citicoline group and 35.6% in the placebo group. For all other scales the rate of improvement ranged from 37.3% to 86.5% in the citicoline group and from 42.7% to 84.0% in the placebo group. Statistically, the citicoline and placebo groups did not differ significantly at the 90-day evaluation: global odds ratio (OR) was 0.98 (95% confidence interval CI 0.83 - 1.49); in addition, in the 2 severity subgroups there was no significant treatment effect (global OR was 1.14 (95% CI 0.88 - 1.49) and 0.89 (95% CI 0.72 - 1.49) for moderate/severe and complicated mild TBI, respectively. At the 180-day evaluation, the citicoline and placebo groups did not differ significantly in relation to the primary outcome: global OR was 0.87 (95% CI 0.72 - 1.04). In accordance with the results obtained, the au-

thors concluded that among patients with traumatic brain injury, the use of citicoline compared with placebo did not lead to improvement in functional and cognitive status. Having analyzed the data from this trial, JJ Secades [40] noticed a number of methodological issues that question seriously the validity and applicability of the results obtained, in particular, is the sample size calculation (OR of 1.4 as the effect of the treatment, which was chosen in accordance with the sample size, rather than basing it on the effects of the drug). Another point of doubts was heterogeneity of TBI: authors mixed different populations, confusing mild, moderate and severe TBI, they also didn't consider localization and pathophysiology of the injuries as well as trajectory for recovery in these groups (sample heterogeneity is considered to be an important confounding factor in the analysis and interpretation of the data). Also, oral administration of citicoline used in this trial is atypical and not approved in some countries, additionally is not appropriate for many of the patients enrolled in the study. One more point of controversion in this trial is poor patient treatment compliance (compliance of only 44.4 of patients having taken 75% of the medication).

Taking into account the controversial data obtained after COBRIT trial results publication, a meta-analysis [40] was conducted to evaluate the real effectiveness of citicoline treatment in patients with TBI. A systematic search was performed on Medline, Embase and Ferrer databases (a drug marketing company represented in several countries) to identify all published, unconfounded, comparative clinical trials of citicoline in acute phase TBI patients. To be included in the meta-analysis, the study must assess the effect of citicoline in the acute phase of TBI, be comparative and have independence outcomes, evaluated with the help of Glasgow Outcome Scale or similar scales. All trials with patients randomization of any age or sex were included. No restrictions were applied in regard to doses, way of administration or duration of treatment as well as publication language, date or publication status. The primary efficacy measure was functional patient independence at the end of a scheduled follow-up period, evaluated as a score of 4 - 5 points of Glasgow Outcome Scale, reflecting an excellent outcome or outcome with mild sequences, that guarantee an independence status after the TBI. The systematic search revealed 23 clinical trials, but only 12 were considered valid for the meta-analysis. There were 2706 patients with mild, moderate, or severe TBI involved in the studies treated in the acute phase with citicoline or not. The doses of citicoline ranged from 250 mg to 6 g per day. The drug was administrated orally or parenterally. The duration of treatment was 90 days. According to the formal meta-analysis principles, based on random effect model, the use of citicoline was associated with a significant increase in the rates of independence with an OR of 1.815 (95% CI = 1.30 - 2.530), but also a significant heterogeneity (I^2 = 54.6%; p = 0.001) was detected, reflecting the 34 years time gap between the studies included in the meta-analysis. Recently a new meta-analysis has been published [41] showing neutral effects of CDP-choline in the treatment of patients with TBI. In recent years, a number of studies have also been published showing a significant effect of citicoline on the recovery of patients with severe TBI [42], especially with diffuse axonal injury [30-43].

Conclusion

Cytidine 5-diphosphocholine (CDP-choline, or citicoline) is an essential intermediate in the synthesis of structural phospholipids in cell membranes, phosphatidylcholine in particular. Following oral or parenteral administration, citicoline breaks down into two main components, cytidine and choline. When taken orally, it is almost completely absorbed and the bioavailability is thus about the same as when it is administered intravenously. Citicoline passes through the BBB and reaches the CNS, where it is incorporated into the membrane and microsomal phospholipid fraction. Citicoline stimulates the biosynthesis of structural phospholipids of neuronal membranes, increases brain metabolism and affects various neurotransmitters levels, in particular norepinephrine and dopamine. In studies conducted in patients with TBI, citicoline accelerated recovery from post-traumatic coma, improved gait, and improved final functional outcome. Citicoline also has a favorable effect in amnestic mild cognitive impairment after mild TBI, including so-called post-concussion syndrome.

Conflict of Interests

None.

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