

Citicoline in the Treatment of Cognitive Impairment

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Abstract

Vascular cognitive impairment is a process which is more frequent in patients with cardiovascular risk factors. The etiology of this kind of impairment could be related to different types of cerebrovascular disorders, given that silent cerebral infarctions or microinfarcts, correlated with small vessel disease, are one of the principal etiologies. Microinfarcts, associated with small vessel diseases, should be considered one of the possible causes of clinical suspicion in patients with cardiovascular risk factors who are asking for help for cognitive complaints. Among the proposed treatments for cognitive impairment there is citicoline. This is an updated review of the possible use of citicoline in the treatment of cognitive impairment.

Keywords

Mild cognitive impairment, Pharmacological treatment, Citicoline

Introduction

Phospholipids are essential constituents of cells, with a high turnover rate to ensure adequate function of cell membranes, especially neuronal membranes [1-3]. Among the main phospholipids in humans are phosphatidylcholine [4]. The main function of the phospholipids is to be part of cell membrane structures and ensure the functions of the membranes [1]. Additional specific functions of the neuronal membrane include nerve impulse conduction and neurotransmission [5]. In the Central Nervous System (CNS) there are various conditions involving phospholipids that can lead to an impairment of functions [6], such as brain maturation [7-10], neurite growth and neuronal regeneration [11]. Impaired phospholipid metabolism has been implicated in the development of traumatic brain injury (TBI) [12-21] and cerebral ischemia [22-37]. Also the phospholipid metabolism has been involved in brain aging [38-40] and certain neurodegenerative diseases [33, 41-53]. Phospholipids also participate in neuroplasticity mechanisms [54], and in conditions involving changes in neurotransmission [55-58], excitotoxic aggression [59, 60] and apoptosis [57-66]. In this context, there is a need to have drugs which act on the membrane structure phospholipids in such situations [67-72].

Citicoline or cytidine-5'-diphosphocholine (CDP-choline) is an essential intracellular precursor of phospholipid phosphatidylcholine [73-87]. The endogenous formation of this compound from phosphorylcholine is the rate-limiting step of this biosynthetic pathway [77, 88-100]. Thus CDP-choline is considered an exogenous source of choline and cytidine, with relevant biochemical actions [101, 102].

Experimental Data

Citicoline has an extensive effect on the cholinergic system and could act as a choline donor to increase the synthesis of acetylcholine. The central cholinergic activating effect of citicoline has been emphasized, with this effect explaining the cardiovascular [103-110], metabolic [111-118], and antinociceptive effects [119-121] of the drug, together with effects on signaling systems [122-127].

Citicoline partially restored learning performance in rats under hypobaric hypoxia [128] or chronic cerebral hypoperfusion [129]; this suggests that citicoline could have a cholinergic action on the mechanisms participating in cognition [130]. Citicoline attenuates vascular cognitive impairment in animal models of brain ischemia [131]. Citicoline also prevents amnesia induced by scopolamine [132-134]. Citicoline acts as a drug able to enhance memory in animals with memory deficits from different causes [135-140].

Citicoline improves phospholipid metabolism in aging models [141-143], is able to restore the activity of acetylcholinesterase and Na⁺/K⁺ pumps [144, 145], and controls the levels of platelet activating factor in the brain [145-147]. Citicoline also offers beneficial actions on brain metabolism [143, 148-150] and on neuroendocrine functions [151-153] in experimental models of brain aging, showing effects such as neuroprotection [154-160], and sharing immunomodulatory [161], and antiapoptotic effects [162, 163] in models of neurodegeneration. Several studies corroborated the positive effects of the drug on aged animals [137, 164, 165].

Another mechanism investigated has been the participation of Sirtuin1 in the neuroprotective/neurorestorative actions of CDP-choline [166]. Treatment with CDP-choline increased Sirtuin1 protein levels in brain concomitantly to neuroprotection. Treatment with sirtinol blocked the effect of CDP-choline, whereas resveratrol elicited a strong synergistic neuroprotective effect with CDP-choline. CDP-choline failed to reduce infarct volume in Sirt1^{-/-} mice. These results demonstrate a robust effect of CDP-choline like Sirtuin1 activator by up-regulating its expression.

It has been demonstrated that citicoline significantly increased dopamine levels and synthesis rate in the striate [167], by means of an action on tyrosine hydroxylase activity, leading to an inhibition of dopamine reuptake [168, 169]. The effects of citicoline on dopamine levels have been shown by other authors [170-173].

Effects on the levels of other neurotransmitters have been reported by other authors [174-178]. The action of citicoline upon the dopaminergic system has also been studied by investigating its pharmacological actions in many experimental models [179-193]. Citicoline increases norepinephrine release [194], influences the relationship between glutamate and GABA [195], and increases the levels of vasopressin [196] and other pituitary hormones [197, 198].

Thus the effects of citicoline on the cholinergic system, together with the other actions on other neurotransmitters and its neuroprotective/neurorestorative properties, could explain the

effects of the drug in improving cognition in patients affected with cognitive impairment of various causes. This also could be due to the role of citicoline in augmenting the efficacy of endogenous brain defense and neuronal repair mechanisms [131].

Clinical Studies

Various experimental investigations on the so-called brain aging have led in recent years to give an increasing importance to changes in cerebral metabolism as a crucial factor involved in the pathophysiology of this processes. In the senile brain there is a general decrease in energetic metabolism and changes affecting lipid and nucleic acid metabolism. Changes in certain neurotransmitters, especially acetylcholine, and hormones are associated in brain aging processes [199], and more recently there have been several publications showing an increasing evidence of vascular risk factors as key mechanisms in the development of cognitive impairment and dementia [200-202]. It has been demonstrated that a worse overall cardiovascular risk profile is associated with poorer cognitive function and this association could be present in young adults from 35 years old [203]. It is also known that these cardiovascular risk factors are associated with smaller brain volumes, in regions identified as early predictors of cognitive decline [204]. Both microinfarcts and lacunar infarcts are associated with small vessel disease of the brain, and this association makes the patients more prone to develop cognitive impairment [205]. Both silent and clinically eloquent strokes are among the most important determinants of dementia in the elderly [200]. But in patients with cardiovascular risk factors without evidence of an eloquent stroke, it is of interest to consider the possibility of the presence of small vessel disease associated or not with microinfarcts, which are normally silent, and their presence is underestimated [206, 207].

Citicoline increases phospholipid synthesis and glucose metabolism at brain level, and influences the metabolism of neurotransmitters. Accordingly, several clinical trials have been carried out to evaluate the effects of CDP-choline in the treatment of cognitive disorders [208, 209]. Citicoline stimulates phosphatidylcholine synthesis in the brain [210-213] and improves the energetic cerebral metabolism of elderly subjects [214]; a fact that is correlated to an improvement on cognitive capacities [215-219]. In healthy volunteers, the administration of citicoline has been associated with improvement in attention [220, 221], memory [222, 223] and in some neurophysiological parameters [224-227].

Many studies have shown the effect of citicoline in the treatment of the so-called senile cerebral involution, decreasing its characteristic symptoms [228-240], especially on memory evaluated by means of various cognitive scales. Other benefits reflected in these studies include improvements in cooperation and capacity of relationship to the environment, and reducing dosage of psychoactive drugs routinely used in psychogeriatrics, with an excellent safety profile. Patients were evaluated using different scales, such as Fishback Mental Status Questionnaire, SCAG, Mini Mental State Examination, Bender-Gestalt test, Hamilton scale for depression, Parkside scale, neurological assessment scale, and attention test.

The use of citicoline in healthy adult individuals induces an increase of growth hormone secretion and a decrease on prolactin secretion [241, 242].

Some positive effects in patients with chronic cerebrovascular disease have also been demonstrated [243-261]. However, in patients with vascular dementia according to current diagnostic criteria, Cohen et al. [262] were not able to show any beneficial effect of citicoline in their pilot study.

Tanaka et al. [263] found a correlation between the cognitive improvement and the increase in cerebral blood flow in patients with vascular dementia treated with the drug. Lozano [264] suggest that citicoline is a safe and effective drug in the long-term course of dementia. Corona et al. [265] concluded that the beneficial effects of the drug in demented patients will be partially explained by the action of the drug on some neurotransmitters systems.

Cacabelos et al. have described several positive effects of citicoline in dementia patients, with improvements on cognitive scales, a significant antidepressant effect, a certain immunomodulatory action, and an increased cerebral blood flow and improved bioelectric activity in the brain [266-269]. The same authors published the results of a double-blind, randomized, placebo-controlled pilot study in patients with mild to moderate senile dementia of the Alzheimer type [270]. Citicoline showed a significant improvement in the cognitive capacity as assessed with the ADAS scale of patients with a positive APOE ϵ 4 genotype. Recently, Feng et al. [271] found that treatment with citicoline may be beneficial for the improvement of network connectivity of the corpus callosum in patients with leukoaraiosis.

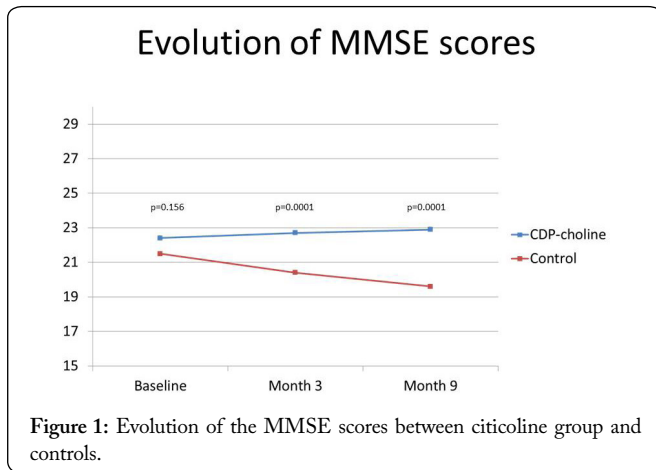
Some authors advocate the use of multifactorial treatments including citicoline in patients with degenerative dementias [272, 273]. Zhuravin et al. [274] demonstrated that the activities of blood serum acetylcholinesterase, butyrylcholinesterase and neprilysin reflect the level of cognitive dysfunction in patients with Alzheimer's disease and can be used as prognostic biomarkers of the level of dementia progression, and that the treatment with citicoline can modify positively these levels.

Fioravanti and Yanagi [275] in their systematic review examined the effects of citicoline in the treatment of cognitive, emotional, and behavioral deficits associated with chronic brain disorders in the elderly. Fourteen studies were included in this review. The type of participants varied over the years and by type of disorders and severity, and ranged from aged individuals with subjective memory disorders to patients with vascular cognitive impairment (mild to moderate), vascular dementia or senile dementia (mild to moderate). In the studies included, the subjects were treated with citicoline for a period of between 20 days and 3 months. The studies were heterogeneous in dose, modalities of administration, and inclusion criteria for subjects, and outcome measures. Results were reported for attention, memory testing, behavioral rating scales, global clinical impression and tolerability. Reaction time was used as a measure of attention, and the results were obtained from seven of the studies with a total of 790 subjects, 384 in the citicoline group and 406 in the placebo group.

Using the standardized mean difference (SMD) and fixed-effect model, the summary effect size is -0.09 (-0.23 to 0.05), meaning there was evidence of a small effect of CDP-choline on attention. The meta-analysis of the memory tests from ten studies included a total of 924 subjects, 456 in the citicoline group and 468 in the placebo group. The effect size on memory was 0.38 (0.11-0.65) which was statistically significant. Using the six studies which reported memory test results in 675 participants with cognitive deficits associated with cerebrovascular disorders, the meta-analysis of memory function revealed homogeneous results and there was evidence of a statistically significant positive effect on memory (SMD = 0.22; 0.07-0.37). Behavior was measured using five different scales in eight studies with 844 subjects, 412 in the citicoline group and 432 in the placebo group. There was evidence of a positive effect of citicoline on behavior (SMD = -0.60; -1.05 to -0.15) using the random effects model. The evidence of a benefit in global impression was stronger; using a fixed-effect model, the Peto OR for improvement in the subjects treated with citicoline as opposed to the subjects treated with placebo was 8.89 (95% CI: 5.19-15.22). Of particular relevance was the finding that citicoline tended to be associated with fewer adverse effects than placebo, but this was not statistically significant. According to the authors, further research with citicoline should focus on longer term studies in subjects who have been diagnosed with currently accepted standardized criteria, especially mild vascular cognitive impairment or vascular dementia.

Deutsch et al. [276, 277] studied the association of citicoline and galantamine in schizophrenia. Also recently some positive effects of citicoline in the prevention of postoperative cognitive dysfunction during total intravenous anesthesia have been reported [278-280]. In a recent study, Li et al. [281] demonstrated the effect of citicoline as an adjuvant therapy for mild cognitive impairment in Parkinson's disease. Kovalenko and Lytvyn [282] demonstrated that citicoline treatment in patients with hypertensive dyscirculatory encephalopathy and concomitant hypothyroidism significantly improves the performance of brain electrogenesis. Putignano et al. published the VITA study [283], a study performed to assess the efficacy of citicoline in elderly patients suffering from stupor related to complex geriatric syndrome, showing that there was an improvement in key measures of performance after the treatment. In the IDEALE study [284] the effectiveness and safety of citicoline in patients with mild vascular cognitive impairment was assessed. The study group received oral citicoline 1 g/d/9 m. MMSE scores improved slightly after the treatment with citicoline, whereas a significant difference was found between the study and control groups at 3 and 9 months (Figure 1). No adverse events were recorded. In this study, citicoline was effective and well tolerated in patients with mild vascular cognitive impairment. The same team published the CITIRIVAD Study [285], with the aim of demonstrating the effectiveness of oral citicoline plus rivastigmine in patients with Alzheimer's disease and mixed dementia. The results show the effectiveness and safety of combined administration versus rivastigmine alone, mainly in slowing disease progression and consequently in disease management, both in Alzheimer's disease and in mixed dementia. In the Citicholinage study

[286] the association of citicoline with an acetylcholine esterase inhibitor was more effective than the acetylcholine esterase inhibitor alone in patients with Alzheimer's disease. These results encourage further investigation of the combined administration on demented patients and the effects on the progression of the disease [287].



Cognitive disorders are common stroke sequelae [288]. Cerebral infarctions are a significant risk factor for vascular cognitive impairment and vascular dementia [289]. In this context, Álvarez-Sabín et al. performed a study to assess the safety and efficacy of long-term administration of citicoline in reducing post-stroke cognitive decline in patients with first-ever ischemic stroke [290]. Cognitive functions improved 6 and 12 months after stroke in the entire group but in comparison with controls, citicoline-treated patients showed better outcomes in attention-executive functions and temporal orientation during the follow-up. The authors concluded that citicoline treatment for one year in this kind of patient is safe and effective in improving post-stroke cognitive decline. These authors published the follow-up to this study after two years of treatment with citicoline [291], adding an evaluation of the quality of life to the cognitive assessment. Age and absence of citicoline treatment were associated with a poorer quality of life. Citicoline treatment improved cognitive status significantly during follow-up ($p = 0.005$), showing a gradual improvement over time. Other authors communicated beneficial effects of citicoline in the treatment of post-stroke cognitive disturbances [292, 293].

León-Carrión et al. [294-296] demonstrated the positive effects of citicoline in a series of studies on post-traumatic memory disorders. Citicoline is considered a valid therapeutic option for the treatment of post-traumatic cognitive impairments [297], also improving the quality of survival [298].

The drug may be more effective for mild cognitive disorders [299-302] and cases related to vascular pathologies [303-306]. In addition, citicoline has been shown to have beneficial effects on some neurophysiological and neuroimmune changes.

Over time there has been an increase in the dosage of the drug, with 1g/d as the recommended dose in recent years. Also, as the bioavailability of the oral drug is almost the same

as that observed with parenteral administration [307], the latest studies have used the oral administration of the drug, which is more convenient for the patients

Conclusions

Cytidine 5'-diphosphocholine, CDP-choline, or citicoline is an essential intermediate for the synthesis of phosphatidylcholine. Citicoline activates the biosynthesis of the structural phospholipids of neuronal membranes, increases brain metabolism, and acts upon the levels of various neurotransmitters. Citicoline improves learning and memory performance in animal models of brain aging. Citicoline is a safe drug without systemic cholinergic effects and is a well-tolerated product. Citicoline protects the brain against ischemic injury, due to its neuroprotective effects but also because the drug can enhance neuroreparative mechanisms, as has been extensively explained by various authors, who consider it to be a suitable treatment for brain ischemia-related disorders and cognitive impairment [304, 308]. These pharmacological characteristics and the pleiotropic mechanism of action of citicoline suggest that it could be effective in the management of cognitive disorders.

In patients with vascular cognitive impairment, citicoline improves the cognitive function, while in patients with degenerative dementias, it is able to stop the progression of the disease.

No serious side effects have been reported related to citicoline [309, 310], and this could be the basis for an empirical (Figure 2) treatment of patients with MCI [311].

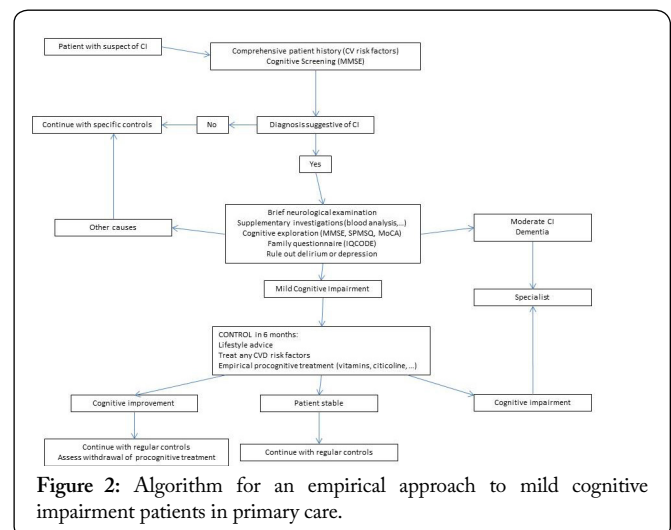


Figure 2: Algorithm for an empirical approach to mild cognitive impairment patients in primary care.

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