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Citicoline, use in cognitive decline: Vascular and degenerative

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ABSTRACT

CDP-choline has been widespread used in humans for decades as a treatment for many types of cognitive impairment. Despite this, its mechanism of action still remains unclear, but several experimental models in acute cerebral ischaemia suggest that it could have a brain repair action. Due to the lack of significant adverse effects and its high tolerability, there has been a growing interest for this molecule in recent years.
In this article, a review of the most significant published clinical trials in cognitive decline has been made. A few Citicoline trials have studied its effects at medium and long-term on vascular cognitive impairment and Alzheimer's disease. Results show that Citicoline seems to have beneficial impact on several cognitive domains, but the methodological heterogeneity of the these studies makes it difficult to draw conclusions about these effects. New trials with a greater number of patients, uniform diagnostic criteria for inclusion and standardized neuropsychological assessment are needed to evidence with much more consistency Citicoline efficacy upon cognitive disorders. The use of new neuroimaging procedures in current trials could be of great interest.

1. Introduction

CDP-choline is an intermediate in the biosynthesis of phosphatidylcholine which is composed of two essential molecules, cytidine and choline [1]. Several effects are likely to contribute to the neuroprotective actions of CDP-choline [2] and include prevention of fatty acids release [3], stimulation of PtdCho synthesis, preservation of cardiolipin and sphingomyelin levels [4], increase of glutathione synthesis and glutathione reductase activity [1], restoration of Na^+/K^+-ATPase activity [5,6], antiapoptotic effects [7,8], among others. All these data suggest that citicoline could decrease structural cell damage [9] caused by ischaemia. For this reason, it has been used by clinicians during decades as a treatment for cerebrovascular diseases, as well as for many cognitive disturbances, including traumatic brain injury or cognitive decline in the elderly. Its brain protective properties besides the good profile of adverse events have increased the interest in the last years about this molecule as a treatment for cerebrovascular and neurodegenerative diseases [10].

2. Citicoline pharmacological data

2.1. Animal models

Radioactive tracer studies in rats show that, after IV administration of radioactively labeled citicoline, labeled phospholipid concentrations in the brain increase steadily over the next 10 h and remain high at 48 h. Exogenous citicoline achieves wide distribution throughout the brain. In a mouse study, 24 h following administration of labeled citicoline, the tracer was widely incorporated in the cortex, white matter, and central gray nuclei. Eventual elimination of administered citicoline occurs very slowly, with small amounts exiting each day by the urinary, fecal, and respiratory routes. Citicoline exhibits a very low toxicity profile [11]. In preclinical studies, a lethal oral dose could not be determined because no deaths occurred at the maximum possible oral dose. No toxic effects were observed in 30-day subacute and 6-month chronic administration toxicity studies of oral citicoline in rodents and dogs. No changes occurred in blood chemistry, organ histology, or neurological or urinary parameters.

2.2. Humans

When infused intravenously in humans, citicoline is rapidly hydrolyzed to choline and cytidine for delivery to tissues throughout the body. In healthy volunteers, at the end of a 30-minute infusion, plasma levels of citicoline are already virtually undetectable, whereas choline and cytidine levels are at a peak, with continued elevated circulating concentrations for the following 6 h. Though not as rapid as intravenous (IV) administration, oral administration also provides an efficient means of delivery, with choline and cytidine plasma levels peaking 2 h after a single oral dose. Passage across the blood-brain barrier is efficient. In humans, in multiple formal clinical trials with prospective monitoring, no categories of serious adverse events have been reported to have an increased frequency in active study arms. Uncommon nonserious adverse effects include gastrointestinal

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distress, restlessness, and irritability, generally within the first few days of treatment. A large drug surveillance study analyzed the safety profile of citicoline in 2817 patients, predominantly elderly individuals treated for Alzheimer and vascular dementia, with treatment duration ranging from 2 to 9 weeks. Only 5% of patients reported adverse effects; gastrointestinal distress was most common (3.6%), and no patient needed to discontinue therapy due to side effects.

3. Experience with citicoline in several pathological conditions: experimental and clinical data

Several reports have so far explored the brain protective effects of CDP-choline in "experimental" stroke. At the experimental level, CDP-choline has been reported to decrease infarct volume and oedema, and/or to improve neurological deficits, either alone or in combination with other agents [12,13,14]. In our laboratory when citicoline (250 mg/kg) was used in combination after rt-PA therapy , there were significant reduction of infarct volume and neuronal death together with a reduction of mortality due to brain damage and moderate improvement in clinical outcome [15]. Moreover, we have studied, in a rat model of embolic ischemic stroke, the effects of high doses of citicoline (1000 mg/kg) considering different lesion markers and our study observed thas higher doses of citicoline produced a greater reduction of brain damage than did low doses [16,17]. In several animal stroke model studies, coadministration of citicoline and fibrinolytics (including tissue plasminogen activator and urokinase) increased the reduction in infarct size attained by the fibrinolytic alone [15,18].

Exogenously administered citicoline accelerates phospholipid synthesis and neural repair. Among animals treated with citicoline in stroke models, motor recovery was greater and motor neurons structurally showed enhanced dendritic complexity and spine density, suggesting that choline precursor therapy increased plasticity within noninjured regions, mediating functional recovery [19].

The use of CDP-choline with this purpose, not only in stroke, but also in other neurological disorders in which an altered function or expression of EAAT2 has been described, as epilepsy [20], Alzheimer's disease [21,22], Huntington's disease [23] and amyotrophic lateral sclerosis [24,25], among others. Citicoline appears to have a benefit, as concluded in a meta-analysis of pooled data from phase III trials [24,26,27]. The advantage is that there are less undesirable effects such that the safety profile seems to be excellent.

3.1. Vascular cognitive decline

Vascular dementia is a heterogeneous condition which includes many different neuropathological entities, such as stroke, brain haemorrage, lacunar infarcts, amiloid angiopathy, etc. Besides, amiloid plaques are a common finding in the pathologic exam of these patients. Nowadays, the pathogenic pathways of vascular dementia both Alzheimer's disease are still unknown.

Injury to cholinergic transmission pathways with decreased release of acetylcholine could contribute to cognitive deficits after stroke. Although cholinergic deficit supposed to be involved in the phisiopathology of vascular dementia is of little magnitude [28,29], cholinesterase inhibitors seem to mildly improve cognitive symptoms in these patients. Up to date, efficacy of cholinesterase inhibitors has been proved in only four clinical trials (two for Donepezil [30,31], one for Galantamine [32,33] and another one for Rivastigmine [34,35], and another two clinical trials studied efficacy and safety of memantine in mild to moderate diseases [36] with similar results.

Because citicoline serves as a choline donor in the biosynthesis of acetylcholine, we made a search over the scientific databases Cochrane and Medline, for the terms: "CDP-choline", "citicoline", "vascular dementia" and "cognitive impairment"; and selected the most representative reviews and original articles.

Fourteen clinical trials were revised in the most recent Cochrane Review [37]. All of them were randomized, placebo-controlled, and a total 1051 patients were enrolled. The total daily dose of citicoline ranged from 100 mg to 1000 mg daily, with a duration of the treatment of 1 to 3 months. The main variables assessed by the investigators were attention, memory and behavior, clinical global function and tolerability and adverse effects profile. We must consider certain heterogeneity between the studies in terms of inclusion criteria (age threshold, diagnostic methodology…), duration of treatment, outcomes in the variables studied, etc, because the trials included have been carried along three decades. Over these years new diagnostic criteria for vascular dementia have been published (NINDS AIREN criteria, 1994) [38]and clinical trials methodology has changed. The total 1051 patients included had different diagnoses (chronic cerebrovascular disease with or without senile dementia, cognitive impairment related to the elderly, Alzheimer's disease and memory complaints). To minimize any possible bias due to the different procedures employed for evaluating cognitive variables, investigators used the standardized mean difference (SMD) and the random effects model. There is evidence of a positive impact of citicoline on memory and behavior in patients with cognitive impairment associated to chronic cerebrovascular disease in a medium term (Table 1). The most significant results are following:

- Attention: Seven trials were reviewed for the effects of citicoline on attention, measured mainly as time reaction tests. 790 patients were included (384 treated with CDP-coline and 406 in the control group). There is no significant evidence of beneficial effects, with a little total effect size: SMD = −0.08 (−0.23 to 0.06), p = 0.5852.
- Memory: The nine trials reviewed included 894 patients (441 treated with CDP-coline and 453 treated with placebo) with different diagnostic categories that ranged from vascular dementia to senile dementia and subjective memory complaints in the elderly. The analysis showed positive effects of citicoline on memory, with a statistically significant magnitude of the effect: SMD = 0.38 (0.11 to 0.65). The six trials focused in cognitive impairment due to chronic cerebrovascular disease revealed a statistically significant positive impact on memory: SMD = 0.22 (0.07 to 0.37).
- Behavior: 814 patients from seven clinical trials were included in this analysis (397 treated with CDP-coline and 417 treated with placebo). There is evidence of a statistically significant but modest beneficial effect of citicoline on behavior: SMD = −0.26 (−0.49 to −0.04).
- Clinical Global Impression: 217 patients from four trials were included (115 treated with CDP-coline and 102 treated with placebo). According to fixed effects model, the Peto odds ratio for improvement in the citicoline-treated group was 8.89 (5.19, 15.22).
- Tolerability: Adverse effects profile was evaluated in seven trials, with a total of 891 patients included (452 treated with CDP-coline and 439 treated with placebo). According to the fixed effects

Table 1
Citicoline in vascular cognitive impairment. Summary of results. From Fioravanti et al. [34].

	No. of trials	No. of patients	Evidence favorable
Attention	7	790	SMD = −0.08 (−0.23, 0.06)
Memory	9	894	SMD = 0.39 (0.10, 0.68)
Memory (cerebrovascular subgroup)	5	645	SMD = 0.21 (0.06, 0.37)
Behavior	7	814	SMD = −0.26 (−0.49, −0.04)
Clinical global impression	4	217	Petto OR 8.89 (5.19, 15.22)
Tolerability	7	891	Petto OR 1.61 (0.98, 2.65)

SMD: standardized mean difference.

model, the Peto odds ratio for no adverse effects in the citicoline-treated group was 1.61 (0.98, 2.65), although it did not reach statistical significance.

Another randomized, double-blind trial studied the effects of citicoline upon cognitive and neuroimaging outcomes, after 12 months of treatment, in patients with vascular dementia. In this trial, 30 patients received 1000 mg of citicoline or placebo daily. MRI was performed at baseline and at 12th month visit. MRI outcome measures were total volume of periventricular hiperintensity and whole brain volume. Neuropsychological assesment explored global functioning, executive functions and attention, memory, visuospatial skills, language and psychomotor skills. It was performed at baseline, 6th and 12th month visits. There were no signifficant differences on cognitive and MRI measures between citicoline-treated and placebo group at the end of the study [39].

Another cholinergic precursor, choline alphoscerate, has been tried in some clinical studies on neurodegenerative both cerebrovascular disease. In preclinical studies, choline alphoscerate increases the release of acetylcholine in rat hippocampus, facilitating learning processes [40]. This activity has been documented in human brain *in vivo*.

A recent review [41], included most of the clinical trials focused on choline alphoscerate in neurodegenerative and cerebrovascular disorders. Six trials (three homogeneous-case and three combined-case) included a total of 789 patients with vascular dementia. Choline alphoscerate dose ranged from 1000 to 1200 mg/day for 3 to 6 months. All of them showed improvement on memory and attention impairment.

Choline alphoscerate has also proved a positive effect on cognitive and motor recovery after a 6 months period of treatment after an acute stroke in three uncontrolled studies [41]. Nevertheless these type of studies have low clinical relevance.

In order to design trials with more homogeneous cohorts of patients, it would be of great interest to identify patients at high risk of developing dementia after a stroke. Helpful predictors to detect predisposed patients could be old age, history of previous or recurrent stroke, and a multiple domain mild cognitive impairment with amnestic component at the poststroke cognitive evaluation [47].

3.2. Degenerative: Alzheimer's disease

As loss of neuronal and glial membrane integrity is a final common pathway of cell injury arising from many disease processes, citicoline has been tested in a wide variety of neurologic conditions aside from focal stroke and vascular dementia.

Most of the studies on cognitive impairment have focused on "late-life cognitive", and have enrolled both patients with vascular cognitive impairment, mixed dementia and Alzheimer's disease. Several small trials have been conducted, but their interpretation is challenging. A few number of trials have investigated only isolated Alzheimer's disease patients or less well-defined cohorts with "senile dementia." The most recent Cochrane review of these studies identified 14 trials enrolling a total of 1051 patients and concluded that there was some evidence of a positive effect upon memory, behavior, and global functioning, though not on attention [37]. Additional trials using modern, standardized diagnostic criteria for patients selection were recommended.

One double-blind, randomized placebo-controlled clinical trial enrolled 30 patients with mild to moderate Alzheimer's disease [48] to study the potential beneficial effect of citicoline upon memory. Patients underwent neuropsycologic evaluation at baseline and at the end of the study. The treatment period with citicoline 1000 mg vs placebo lasted for twelve weeks. Citicoline-treated group showed better cognitive performances vs placebo group did. Cognitive measures included ADAS (and ADAS-cog) and clinical global impression included CIBIC+. The magnitude of improvement was greater in Alzheimer's disease APOE E4 patients with mild dementia (GDS<5), with a statistic signification of $p<0.01$ for cognitive assessment and $p<0.05$ for functional assessment. Furthermore, no significant adverse effects nor biological or haematological parameters were reported in citicoline-treated group.

Choline alphoscerate has also been tried as a treatment for degenerative dementia [41]. This review analyzes six clinical trials, with a total of 565 patients with mild to moderate dementia, who received 1000 to 1200 mg/day of choline alphoscerate for 3 to 6 months. Outcomes in memory and attention were better in the treated group vs the placebo group (Table 2).

A newer study evaluated 261 patients wit mild to moderate Alzheimer's disease demonstrated statistically significant better outcomes in cognitive parameters after 180 days of treatment (ADAS-Cog, MMSE, GDS, ADAS-Behav, ADAS-Total, and CGI) in the treated group vs the placebo group. A comparison of ADAS-Cog analysis form this assay with the same item in four trials with donepezil shows a positive trend in favor of choline alphoscerate [41].

4. Next steps

Viewed from a current clinical translational research perspective, multiple potentially fruitful approaches await application to this agent. Despite the positive results in these studies we cannot generalize them due to methodologic differences. However they justify reconsideration of citicoline in larger controlled trials.

Table 2
Comparison among citicoline, choline alphoscerate and donepezil in neurodegenerative Alzheimer's type cognitive impairment. Summary of trials.

	No. of patients	Duration	Treatment, dose	Cognitive measures	Evidence favorable	Adverse effects
Alvarez et al. [7]	30	12 weeks	Citicoline; 1000 mg daily; Placebo controlled	ADAS, ADAS-cog, CIBIC+	ADAS-cog difference between groups: −2.3 ($p<0.05$)	No signifficant adverse effects
De Jesus Moreno [42]	261	24 weeks	Choline alphoscerate; 1200 mg daily; Placebo controlled	ADAS, ADAS-cog, MMSE, GDS, CGI	ADAS-cog difference between groups: −3.2 ($p<0.001$)	No signifficant adverse effects
Rogers et al. [43]	141	14 weeks	Donepezil; 1.5, 3 and 5 mg; Placebo controlled	MMSE, ADAS-cog,	50% reduction of cognitive decline in treated group	No signifficant diferences with placebo
Rogers et al. [44]	473	30 weeks	Donepezil; 5 and 10 mg; Placebo controlled	ADAS-cog, CIBIC+, MMSE, CDR-SB, QoL	ADAS-cog difference between groups: −2.49 to −2.88 ($p<0.0001$)	Cholinergic effects were signifficantly higher in treated groups, but mild and/or transient
Rogers et al. [45]	468	15 weeks	Donepezil; 5 and 10 mg; Placebo controlled	ADAS-cog, CIBIC+, MMSE,	ADAS-cog difference between groups: −2.5 to −3.1 ($p<0.001$)	68–78% No signifficant diferences with placebo
Burns et al. [46]	818	30 weeks	Donepezil; 5 and 10 mg; Placebo controlled	ADAS-cog, CIBIC+, CDR-SB, IDDD	ADAS-cog difference between groups: −1.5 to −2.9 ($p<0.0001$)	79–86% Slightly higher than placebo group

The success of future trials will depend on an accurate selection of the sample. As said before, in relation to vascular cognitive impairment studies, patients eligible should have a homogeneous risk profile to develop dementia. For this purpose, appropriate and standardized tools of neuropsychological evaluation should be used, together with neuroimage techniques [49].

To probe whether citicoline enhances beneficial reorganization and remapping of motor and cognitive functions after initial injury, studies using functional MRI, voxel-based morphometry, diffusion tensor imaging, and MR spectroscopy would be of great interest [9].

In conclusion, it is essential to carry out new trials with more homogeneous parameters (diagnostic inclusion criteria and standardized neuropsychological assesment), new neuroimaging techniques and a larger number of patients to establish the efficacy of this molecule on cognitive impairment either vascular or degenerative.

Disclosure statement

E. Díez-Tejedor has collaborated as a clinical advisor, investigator in clinical trials or as speaker with the following companies: AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Cellerix, Ferrer Grupo, Knoll, Lilly, Parke-Davis, Pfi zer, Sanofi -Synthelabo, Servier, UCB Pharma, Uriach, and EBEWE NeuroPharma.

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