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Short Communication

Citicoline in Vascular Cognitive Impairment: Some Latest Evidences

Introduction

CDP-choline (cytidine-5′-diphosphate choline), also called citicoline, is one of the most frequently prescribed drugs for cognitive impairment in several European countries and worldwide [1–3].

In clinical practice, a number of different studies have shown that citicoline is effective in Parkinson's disease, glaucoma, amblyopia, head trauma and cognitive impairment (CI) of diverse etiology, such as in CI following cerebrovascular disease [1-4].

Citicoline is able to inhibit apoptosis associated with cerebral ischemia and several models of neurodegeneration [1–3]. It can also potentiate neuroplasticity and is a natural precursor of phosphatidylcholine, one of the most important structural phospholipids in the neuronal membranes. Furthermore, since it is formed by choline, it works for biosynthesis of acetylcholine [1–3], CDP-choline increases cerebral metabolism, noradrenaline, and dopamine levels in the central nervous system (CNS) [1,4].

A great amount of evidences derive from animal studies suggesting that exogenously administered CDP-choline is neuroprotective. Indeed, it may accelerate resynthesis of phospholipids and attenuate the progression of ischemic cell damage by suppressing the release of free fatty acids [2]. Several studies have shown that it can have beneficial effects both in degenerative and in vascular cognitive decline [5–10].

Until now one of the most critical points about the effectiveness of citicoline was linked to the relatively short term of clinical studies, which usually lasted for no more than 3 months, a too short time for appreciating its real effects. One of the studies which recently showed the opportunity of prolonged administration for getting the best outcomes (9 months) was the IDEALE Study [11].

The "Studio di Intervento nel Decadimento Vascolare Lieve" (IDEALE study) was an open-label, multicenter, Italian study, the aim of which was to assess the effectiveness and safety of oral citicoline (1 g/day) in elderly people with mild vascular cognitive impairment.

It was performed on 387 elderly patients selected from six Italian regions and included subjects aged ≥65 years old, with Mini Mental State Examination (MMSE) ≥21, or subjective memory complaints but no evidence of deficits and vascular lesions on neuroradiology.

265 patients were assigned to open-label treatment with oral citicoline 500 mg twice a day in a fasting state, 84 patients to no treatment (controls). The two groups were superimposable regarding mean age, mean MMSE values, comorbidities and pharmacological treatment for other diseases.

An assessment was made at baseline (T0), after 3 months (T1), and after 9 months (T2). The MMSE score in the treated group remained essentially unchanged over time (22.4±4 at T0; 22.7±4 at T1; 22.9±4 at T2). A mild improvement of 0.5 points on average was found after the 9 months of the study. Importantly, the untreated group showed a decline in MMSE score over the 9 months (21.5 at T0; 20.4 at T1; 19.6 at T2; -1.9 points between T0 and T2). Furthermore, a significant difference in MMSE scores was found between the treatment and control groups at T1 (P 0.0001) and T2 (P 0.0001) time points, but not between T0 and T1 or between T0 and T2 in the active group [11].

However, a strong contribution to understand the long-term effects of citicoline treatment in vascular cognitive impairment was given by two papers by Alvarez-Sabin and coworkers (2013; 2016) [12,13] .

The first study by Alvarez-Sabin and coworkers (2013) showed the safety of 12-month citicoline treatment (1g) and its possible efficacy on stroke outcomes, particularly cognitive function, on 347 patients with first-ever ischemic stroke [12].

In conclusion, the study by Alvarez-Sabin and coworkers was the first study to demonstrate that citicoline treatment for

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12 months post stroke is a safe alternative and offers remarkable benefits in improving post stroke cognitive impairment and in preventing cognitive decline.

The second study by Alvarez Sabin and coworkers (2016) was aimed to know the effect of citicoline treatment in quality of life (QoL) and cognitive performance in the long-term (two years) in patients with a first ischemic stroke [13].

It was an open label randomized parallel study of citicoline (1g day orally) vs. usual treatment, where patients were selected 6 weeks after a first ischemic stroke and randomized into parallel arms.

163 patients were followed during 2 years, mean age was 67.5 ± 10.7 years old, and 83 (50.9%) were women.

The study demonstrated that long-term treatment with 1g oral citicoline is able to improve cognitive status of stroke patients and is associated with a better quality of life two years following a first ischemic stroke [13].

These studies were remarkable because they showed that citicoline is safe and effective in neuroprotection and neurodegeneration through a number of different mechanisms, including the activation of a group of important proteins, called sirtuins [14,15].

Other important and recent studies showed that citicoline is safe and effective in vascular cognitive disorders and also in neurodegenerative disorders such as Alzheimer's disease when associated with cholinesterase inhibitors [16,17].

In conclusion, citicoline at the dosage of 1g daily and given orally, due to its high bioavailability (approximately 90%) [4], is effective in cognitive impairment, especially vascular CI and post stroke CI. Chronic administration (from 6-9 months up to 2 years) is not only safe, but also one of the main requisites for its effectiveness, because it promotes some remarkable neurobiological paths (biosynthesis of neuronal membrane phospholipids, activation of sirtuins, increase of intrasynaptic acetylcholine and of amines in the CNS (noradrenaline, dopamine), thus leading to neurorepair and neuroprotection).

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