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Citicoline as Add-On Treatment in Alzheimer's Disease: Tips from the Citicholinage Study

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Abstract

The Citicholinage Study was an Italian multicentric, retrospective study showing the effects of combination treatment of a cholinergic precursor, citicoline, with acetylcholinesterase inhibitors (AchEI) (donepezil, rivastigmine and galantamine) in Alzheimer's disease (AD) patients.

This was the first study which assessed the possible role of citicoline associated to a cholinesterase inhibitor, used for at least 9 months, at the maximum tolerated dosage. It involved 448 patients aged 65 years old or older, 251 treated with combination therapy vs. 197 treated with the only AchEI, mostly donepezil and rivastigmine.

Patients in combined treatment showed a statistically significant increase in MMSE between T0 and T1 (16.88 ± 3.38 versus 17.62 ± 3.64, respectively, p=0.000) and between T1 and T2 (17.62 ± 3.64 versus 17.83.54 respectively, p=0.000). The association citicoline plus donepezil showed to be still better than citicoline plus rivastigmine. Definitely the present study showed that a cholinergic precursor such as citicoline plus an AchEI is able to slow down disease progression in AD patients.

Keywords: Citicoline; Acetylcholinerase inhibitors; Alzheimer's dementia; Acetylcholine; Cholinergic precursors

Introduction

Citicoline or CDP-choline (cytidine-5'-diphosphate choline), is one of the most frequently prescribed drugs for cognitive impairment in several countries worldwide [1-3]. It is composed of ribose, pyrophosphate, cytosine (a nitrogenous base) and choline. In clinical practice, a number of different studies have shown that citicoline is effective in cognitive impairment (CI) of diverse etiology, such as post-stroke CI, Parkinson's disease, glaucoma, head trauma and even Alzheimer's dementia (AD) [1-3].

The study was born following some clinical observations, one derived from the ASCOMALVA, an open label, double-blind study, which showed the effectiveness of a cholinergic precursor, choline alphoscerate, associated with donepezil, in slowing down Alzheimer's disease progression vs. donepezil alone [4]. Another study, the CITIRIVAD study, was a retrospective case-control study conducted on 174 consecutive outpatients aged ≥ 65 years old, affected with AD or mixed dementia (MD), mean age 81.3 ± 4.5 years old, treated with rivastigmine patches plus citicoline 1g daily vs. rivastigmine alone. It showed the effectiveness of combined administration, mainly in slowing down disease progression [5].

The Citicholinage Study

Taking into account the examples of the possible role of a cholinergic precursor such as citicoline in cognitive impairment and the contemporary literature, we planned the CITICHOLINAGE Study, that is CITIcoline plus CHOLinesterase INhibitors in AGEd patients affected with Alzheimer's disease.

The Citicholinage study was a retrospective, multi-centric, case-control study on 448 consecutive patients aged 65 years old or older affected with AD (39.03% men, 60.97% women). It was performed in seven Centers for Cognitive Impairment and Dementia in Italy. The aim of the present study was to show the effectiveness of oral citicoline (1 g/day) plus AChEIs (at the maximum tolerated dosage) in patients affected with AD. Group A, (Case), was made of 251 patients (56.02%), treated with an AchEI (donepezil, rivastigmine or galantamine)+citicoline 1 g/day given orally. Group B (Control), was made of 197 patients (43.98%), treated with an AChEI. Patients had been administered Mini Mental State Examination test (MMSE) corrected according to age and education, Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Neuropsychiatric Inventory Scale (NPI), Cumulative Illness Rating Scale (CIRS), Geriatric Depression Scale (GDS)-short form.

Patients had been visited in seven Centers for Cognitive disorders and Dementia of five Italian regions, between January 1st, 2013 and December 31st, 2015. All the tests had been administered at baseline (T0), after 3 (T1), and 9 months (T2).

No differences were present between case and controls at baseline, regarding mean age, tests administered and education. Patients included in the study had to be 65 years old or older and affected with AD. Of the patients treated with citicoline plus AChEI, only those who had been treated for at least 9 months were included in the study; as above mentioned, another important point was that AChEIs were used at the maximum tolerated dosage. Patients treated with other drugs used for AD (i.e., memantine) or other cholinergic precursors (i.e., choline alphoscerate, choline bitartrate or other cholinergic precursors) or other nootropics (such as homotaurine), were excluded from the study.

Our aim was first of all to assess the possible effects of combined administration versus AChEIs given alone on cognitive functions; we also tried to assess the possible differences among the three AChEIs

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combined with citicoline and if combination therapy vs AChEIs alone was associated with adverse events.

Statistical analysis was made by Student's *t* test or the Chi-square test, as appropriate for comparison among groups. Repeated measure ANOVA was applied to assess the differences in changes between data mean values at baseline, T1 and T2. Significant differences were assumed to be present at $p<0.05$. Statistical Package for the Social Sciences (SPSS) software, program version 20.0 for Windows was used.

The results were significant; at baseline no difference was present in MMSE (group A 16,88, group B 16,41); importantly, already after three months MMSE was significantly higher for patients taking combined treatment vs AchEI alone (17,62 vs. 15,99; p=0.000) and the difference was more evident after 9 months (17,89 vs. 15,41 respectively, p=0.000) (Figure 1).

We tried to assess possible differences among the different AchEIs, but we chose to compare patients treated with donepezil vs. patients treated with rivastigmine. Indeed, in the real world, all the seven centers had few patients treated with galantamine. Interestingly, we had 144 patients treated with the combination therapy donepezil plus citicoline vs. 105 patients treated with rivastigmine plus citicoline. Both groups showed an increasing trend in MMSE scores donepezil group (T0 17,15; T1 18,15; T2 18,49), rivastigmine group T0 (16,54; T1 16,89; T2 17,07). At T0 no difference was present (p=0.165); after 3 and 9 months the donepezil group showed a better and significant performance, (T1 p=0,007; T2 p=0,002, respectively), even if we do not have any possible explanations.

There was also an improvement in mood showed at GDS-5 items in the citicoline group (group A), probably because citicoline is able to increase intrasynaptic noradrenaline and dopamine levels and because, following choline metabolism, there is an increase in S-adenosyl-l-methionine levels, which is a serotonine precursor. The role of amines in mood is widely known.

Combined treatment was safe and well tolerated, with no differences vs. the AchEIs alone (restlessness, headache, gastric intolerance) and as reported in the literature they were self-limiting [6]. No significant systemic cholinergic effects following the use of citicoline have ever been reported.

The limitations of the study derive from the fact that it was a retrospective case-control study, conducted on a limited number of patients. An open, double-blind and multi-centric study could even be more incisive in showing the potential benefits of long-term treatment with citicoline and still more incisive wherever treatment is even longer (i.e., one-two years treatment).

Conclusive Remarks

Definitely, what are the main tips from the CITICHOLINAGE Study? Why does citicoline work?

The CITICHOLINAGE study is remarkable because it was the first study on AD patients showing adjunctive advantages from the association of an AChEI with citicoline compared to the AChEI alone. In other words, the association of citicoline to the AChEIs may represent an option to prolong or even potentiate the beneficial effects of cholinergic therapies in AD and slow down AD progression. The improvement between the two groups was already evident after three months and was even more significant after 9 months. Owing to the lack of drugs working on the possible pathogenetic pathways leading to AD, we think it is important to search for effective therapeutic strategies potentially strengthening the present pharmacological means. The use of a valid cholinergic precursor such as citicoline, at the right dosage and for a time long enough (6-9 months, even if results can be clearly shown already after 3 months) is effective in AD patients.

The combination treatment of CDP-choline (or citicoline) with AchEIs in AD seems to prolong their beneficial effects, probably through an increase in acetylcholine intrasynaptic levels and the possible actions on phospholipid synthesis, chiefly phosphatidylcholine, cellular function and neuronal repair, in particular for its actions on neurogenesis, synaptogenesis, gliagenesis and angiogenesis [7,8] (included the restoration of mitochondrial ATPase and membrane Na^+/K^+ ATPase activity and the inhibition of phospholipase A_2 activity) [6]. Mostly it works as a choline source for the biosynthesis of acetylcholine [1-3].

Moreover, treatment with citicoline in mild cognitive impairment and in AD patients results in an increase of the activity of blood serum acetylcholinesterase, butyrylcholinesterase and neprilysin. Neprilysin is a metalloprotease enzyme able to degrade β-amyloid and it is regulated by the protein nicastrine, which is part of γ-secretase [9].

Last but not least, citicoline works thanks to its powerful activation of sirtuin 1, a NAD-dependent protein which deacetylases histones and has been shown to possess protective effects against age-related diseases such as cancer, diabetes, cardiovascular disease and neurodegenerative diseases, such as AD, Parkinson's disease, amyotrophic lateral sclerosis and remarkably, in brain ischemia [10].

Indeed, SIRT1 is protective against A β plaque formation in animal models and is able to activate ADAM10 (α-secretase) transcription, that is the non-amyloidogenic pathway, thus resulting in a reduced production of Aβ [10].

Citicoline appears to be effective in cognitive impairment of any kind, especially vascular, as shown by the IDEALE Study, the CITIRIVAD Study and, by the way, the CITICHOLINAGE Study [5,11,12].

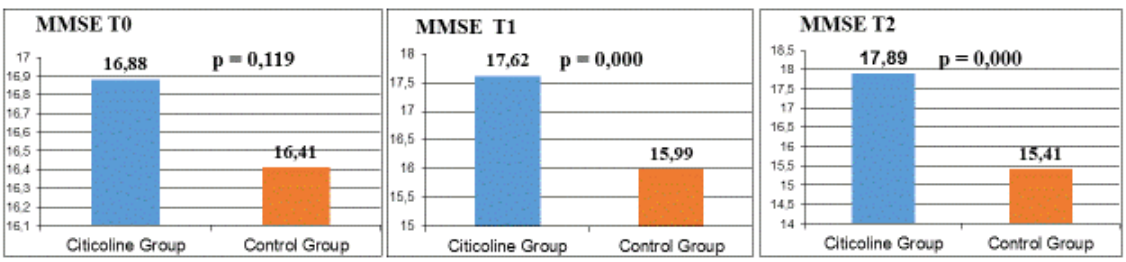

Figure 1: MMSE score at T0, T1 and T2 (citicoline group vs. control group).

The final message from this important study is that a wise use of citicoline at the proper dosage (1000 mg/day) and for the proper time (at least 3-6 months up) is effective also in AD patients and opens a new scenario and new perspectives in the next future for better optimizing treatment in neurodegeneration.

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