

Citicoline (Cognizin) in the treatment of cognitive impairment

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Abstract: Pharmacological treatment of cerebrovascular disorders was introduced at the beginning of the 20th Century. Since then, a multitude of studies have focused on the development of a consensus for a well defined taxonomy of these disorders and on the identification of specific patterns of cognitive deficits associated with them, but with no clear consensus. Nevertheless, citicoline has proved to be a valid treatment in patients with a cerebrovascular pathogenesis for memory disorders. A metaanalysis performed on the entire database available from the clinical studies performed with this compound confirms the experimental evidence from the animal studies which have repeatedly described the multiple biological actions of citicoline in restoring both the cell lipid structures and some neurotransmitter functions.

Keywords: citicoline, CDP-choline, dementia, cerebrovascular disorders

Introduction

Citicoline is the name for cytidine 5'-diphosphocholine (CDP-choline) when this is used as an exogenous sodium salt. In fact, CDP-choline is an endogenous nucleotide naturally found in the body where it is an essential intermediate in the synthesis of the major phospholipid of the cell membranes, phosphatidylcholine (PtdCho). This type of synthesis is called the Kennedy pathway (Fernandez-Murray and McMaster 2005).

As a drug, citicoline has been proposed for use in traumatic brain injuries, stroke, vascular dementia, Parkinson's disease, and brain aging (Blount et al 2002) where it has the function of stabilizer of cell membranes and reduces the presence of free radicals (Zweifler 2002). In particular, there is some evidence of a stimulating role of citicoline for the release of dopamine neurotransmitters in the brain (Fonlupt et al 1985).

Citicoline, by activating the central cholinergic system, also increases plasma adrenocorticotrophic hormone (ACTH) levels and potentiates serum thyrotrophin (TSH) levels. The stimulation of central nicotinic and muscarinic receptors also increases growth hormone (GH) and luteinizing hormone (LH) serum levels (Cavun and Savci 2004). This activity on the cholinergic system is of high therapeutic usefulness in those clinical conditions where alterations of acetylcholine metabolism are considered one of the primary causes of disease (Shen 2004), eg, Alzheimers Disease (AD).

The biological activity attributed to citicoline has suggested a possible role of citicoline on improving memory (McDaniel 2003). Some clinical studies have given evidence to this hypothesis (Agnoli et al 1989; Spiers et al 1996) and there is a proposal for studying citicoline in mild cognitive impairment (MCI) with the aim of confirming both its efficacy in these patients and a possible role as a retardant agent for the cognitive deterioration of the eventual subsequent dementia (Abad-Santos 2002).

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Therapeutic applications of citicoline

Stroke

More than 11 000 people, including patients and volunteers have been studied for evaluating citicoline therapeutic effects. 1372 of these patients were included in studies concerning citicoline efficacy in acute ischemic stroke and pooled together in a meta-analysis of these studies (Davalos et al 2002). This analysis showed that citicoline increases the probability of a complete recovery after three months from moderate to severe stroke when it is administered within 24 hours from the event, although the odds ratio of improving with citicoline is only 1.33. Citicoline's therapeutic action has been attributed to its restoring activity of the PtdCho levels which decrease after a stroke (Rao et al 2006).

In stroke patients there seems to be a particular problem in efficiently delivering citicoline at high enough blood levels required to be effective, and to avoid those differences in results evidenced between studies done by intravenous (IV) administration of the drug and oral administration, a more effective preparation for the oral administration is suggested (Rao and Hatcher 2005).

Vascular dementia

The clinical picture of cognitive and behavioural disorders associated with chronic cerebrovascular disorders (CVD) is much less clear-cut and defined than the picture associated with Alzheimer's dementia. The definition itself of vascular dementia (VD) has been under discussion for a long time and the heterogeneity of the conditions of patients included in this group is probably higher than the similarities between patients (Wallin et al 2003).

Correlative studies

When attempts are made to identify relevant relationships between neuroimaging and cognitive patterns, most of the studies have not been able to point out consistent and reliable concordance between these two domains (Paul et al 2003; Sweet et al 2003; Gunstad et al 2004) primarily because of the low power of these studies due to the small number of cases (Cohen et al 2003).

There is evidence of different patterns of cognitive deficits in patients with chronic cerebrovascular disorders when it has been possible to differentiate between those with prevalent signs of altered hippocampal volume from those with diffuse alterations in the grey and white matter

(Mungas et al 2005). Memory deficits are more relevant in the former group and executive function impairment in the latter group. These findings do not overlap with those that emerge when subcortical dementia is studied as an independent clinical entity characterized by defined quantities of leukariosis. These neuroimaging findings are commonly associated with deficits in executive function, while memory disorders are considered to be a direct function of cortical impairment (Price et al 2005). In some instances, this apparent contrast among study results was explained by the different origin of the patients included; eg, when patients from stroke clinics are compared with patients from memory clinics, the specificity of relationship between neuroimaging and functional data is much weaker in the latter group (Rockwood et al 2006). A proposal has been presented that considers subcortical dementia as a specific form of vascular dementia related to a predominantly small vessel pathogenesis. Mixed dementia is then considered as a nonspecific form of vascular dementia and related to prevalent large infarcts pathogenesis associated with cortical primary atrophy (Jellinger 2004). This model points out the need of considering possible different pathogeneses for different forms of vascular encephalopathy, but does not yet help in identifying specific cognitive patterns of decline associated with them. These issues have largely confounded the studies of citicoline.

Population studies

In studies aimed to identify the relationship between presence of cerebrovascular disorders and prevalence of cognitive disorders in the general population, signs of vascular pathogenesis such as arterial stiffness or generalized atherosclerosis are consistently related to cognitive deterioration which ranges from mild severity to dementia (Hanon et al 2005; Vinkers et al 2005).

Specificity of cognitive deficits

The most common way of defining the specificity of cognitive deficits in vascular dementia is based on comparison with AD patients. Cognitive deficits in these two forms of dementia are consistently found to be more severe in AD patients, while the specificity of deficits in vascular dementia is less clear and more difficult to be replicated in diverse studies. Executive function deficits seem to be more prevalent in vascular dementia, while memory deficits are more typical for AD (Traykov et al 2004; Giovannetti et al 2005; Golden et al 2005).

Another line of research focuses on the identification of specific predictors of developing vascular dementia in groups of patients characterized by those pathologies which are commonly considered as risk factors for cardiovascular pathologies such as diabetes and hypertension. The evidence of slight and not evenly distributed signs of cognitive impairment in hypertensive patients (Fioravanti et al 1991) and its relationship with the daily temporal distribution of elevated picks of systolic blood pressure (more than with the level of high blood pressure of picks) (Fioravanti et al 1996) can be considered as the evidence of a progressive development of a cerebrovascular pathology even before gross anatomical signs of abnormality can be identified in the brain tissues. These findings provide support for the proposal to introduce early therapeutic intervention in patients with mild signs of cerebrovasculopathy or even with risk factors for it (Schindler 2005).

Treatment of cognitive deficits

Attempts to treat symptoms of decline in cerebrovasculopathies have been made since the first years of the last century (Fioravanti 2003) starting with niacin and continue today. At the beginning of the 1980s, citicoline was used in these clinical areas after having been already in use in treatment for stroke. In most of the clinical studies with citicoline in VD, memory has been the principal end point in the efficacy evaluation. There is a large experimental database of experimental studies on memory and learning performed on aged animals treated with citicoline. Most of these studies have shown that treatment with citicoline ameliorates cognitive deficits but does not necessarily improve normal cognitive functions (Conant and Schauss 2004). The few studies done on memory in aged human subjects with memory disorders, but no dementia, have underlined the extreme variability of positive outcomes depending on the type of patients and the kind of measures used in the studies. Memory is a very complex and multidimensional variable to quantify in humans and, consequently, results from different studies which have in common the assessment of memory are not necessarily homogeneous and comparable if the specific modality of memory evaluation is not taken into account. We have seen that those studies which are trying to identify specific patterns of memory disorders in vascular dementia are not yet able to define a definite and reliable cognitive model of functioning of these patients. As a consequence, it is almost impossible to try to systematically apply a specific memory parameter for the evaluation of treatment efficacy in this

clinical area, as it has been possible for AD. There is a possibility that memory disorders might be contaminated by other disorders attributable to executive function including attention. This problem has been examined by looking for methods of evaluating primary memory deficits as distinct from those secondary to other cognitive impairments external to memory per se (Fioravanti and Di Cesare 1992).

Another relevant problem that emerges from a critical analysis of the current and past literature is the relatively poor reliability of single studies performed on small samples of patients with various forms of vascular dementia (a further level of complexity is derived by the different criteria given to these patients in different periods of time). A meta-analysis is the best solution available for circumventing these limitations. In the case of citicoline, a meta-analysis for examining the reliability and validity of effects on memory which have been studied in different ways and types of patients in various studies, could fail to confirm the positive results of the single studies once these data are pooled together.

A meta-analysis has been performed on the available published and unpublished data obtained from controlled clinical trials done with citicoline. This meta-analysis carried out according to the Cochrane Collaboration guidelines is periodically updated in order to include all the studies available (Fioravanti and Yanagi 2005).

Results of the meta-analysis are divided by domains. This allows for a comparative analysis between different areas of assessment; for example, attention and memory. It is possible to verify the homogeneity of results within each domain.

Memory is one of the domains in this analysis and includes results from 884 patients. While studies in this domain include other types of patients as well as cerebrovascular patients, there was no heterogeneity among their results. This indicated that the effect of citicoline on memory was significantly different from the placebo effect, and did not specifically depend on the pathogenesis of the cerebral disorder (effect size 0.19; confidence interval [CI] 95% 0.06, 0.32; $p < 0.005$). In fact, when only cerebrovascular disorders studies were pooled together (for a total of 675 patients), the homogeneity and entity of results was about the same (effect size 0.22; CI 95% 0.07, 0.37; $p < 0.004$).

Within the domain that deals with behavior control and competence (a total of 814 patients), there was a citicoline effect significantly different from placebo and independent

from type of measure and pathology examined (effect size -0.26 ; CI 95% $-0.49, -0.04$; $p < 0.004$). These results coupled with those of the domain clinical evaluation of improvement concerning a total of 217 patients (effect size determined as the odds ratio of improving under active treatment 8.89; CI 95% 5.19, 15.22; $p < 0.001$) showed that the cognitive effects of citicoline are clearly evident at the behavioral level and can be easily appreciated with a clinical observation of patients irrespective of the functional paradigm used to measure them.

The attention domain, even though based on a substantial number of 790 patients, revealed a large amount of variance because of the large individual differences. These data did not permit an interpretation of how much of the results evidenced by memory measures can be considered as specific of the “true” memory processes or as secondary to an effect on other cognitive components of the cognitive decline.

Finally, the tolerability of citicoline has never constituted a problem whatever the modality of administration or the dosage.

Conclusions

Treatment in patients with disorders attributed to a cerebrovascular pathogenesis has a long history. Unfortunately, many problems are still unresolved, including the taxonomy of these disorders and a definition of cognitive pattern of decline to be associated to this taxonomy. These intrinsic problems have not helped to develop accepted methods of research and treatment for these patients. Despite these difficulties and elements of confusion between different clinical studies performed at different periods of time, citicoline has emerged as a valid treatment for patients with chronic cerebrovascular disorders or with memory problems.

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