Citicoline: A Review of a Promising Over-The-Counter Dietary Supplement for Neuroprotection and Neurorepair

William A. Gentry, MPAS, PA-C
Senior Physician Assistant, Neurology
Audie L. Murphy Veterans Medical Center

Abstract

Citicoline (CDP-choline; cystidine 5'-diphosphocholine), a form of the essential nutrient choline is a promising and widely available agent for neuroprotection and neurorepair. Research in animal experiments and human clinical trials provides evidence of its cholinergic and neuroprotective actions. As a dietary supplement, Citicoline appears useful for improving both the structural integrity and functionality of the neuronal membrane that may assist in membrane repair. Studies indicate the potential of Citicoline to improve cognitive deficits, and mental performance in patients with early-stage Alzheimer's disease and age-related dementias, improve stroke rehabilitation, brain and spinal cord injuries, adjunctively treat numerous neurological diseases/conditions, and even be used as a supplemental pharmacotherapeutic agent in improving glaucomatous optic nerve damage.

Introduction

Some of the most prevalent neurological disorders of our time, such as Stroke, Dementia, early-onset Alzheimer's disease, Multiple Sclerosis and even Epilepsy, have neuronal injury and subsequent neurological dysfunction, which is often attributed to destruction or instability of the neuronal membrane, as the underlying etiologic pathology. However, evidence is mounting of a readily available over-the-counter supplement that may promote membrane stability as well as act in the repair mechanism of previously damaged membranes and possibly provide a unique therapeutic option in the treatments of certain neurological disorders. **Citicoline**, is a readily available, over-the- counter psychostimulant/nootropic dietary health supplement. The purpose of this paper is to provide a brief background on citicoline, its biochemistry, pharmacokinetics including its safety profile, and to explore the multiple clinical applications, as well as review the growing evidence of efficacy of citicoline as neurology's potentially, first truly effective neuroprotective and neuro- restorative agent.[1,5] Citicoline, also known as **cytidine diphosphate-choline (CDP-Choline)** and **cytidine 5'-diphosphocholine** is a complex organic molecule that functions as an intermediate in the biosynthesis of cell membrane phospholipids. Closely related to choline, a nutrient commonly put into the B vitamin family, CDP-choline belongs to the group of biomolecules in living systems known as "nucleotides" that play important roles in cellular Metabolism.[1] Citicoline research in animal experiments and human clinical trials provides evidence of its cholinergic and neuroprotective actions. Because Choline precursors promote repair and growth of cell membranes, they provide both structural integrity and functionality of cell membranes and, thus hold promise in a wide variety of neurological disease, including ischemic and hemorrhagic stoke. In fact, in experimental stroke models, citicoline conferred acute neuroprotection and enhanced neuroplasticity and neurorepair in the subacute period.

Although individual human stroke trials have been inconclusive, a meta- analysis of 10 trials, enrolling 2,279 patients receiving citicoline had substantially reduced frequencies of death and disability. Reinvestigation of citicoline with modern neuroimaging and clinical trial methods are underway and will provide more definitive information regarding the mechanistic and clinical effects of this promising neurotherapeutic agent.[2] In addition, other studies suggest that CDP-choline supplements increase dopamine receptor densities,[3] and suggest that CDP-choline supplementation can ameliorate memory impairment caused by environmental conditions.[4] In the United States, citicoline, because it is an agent that is available over- the-counter and without a prescription, is considered a complementary or alternative therapy (CAM) by clinicians and patients, alike. However, unlike many (CAM) therapies, which often are poorly studied or have had short market longevity, citicoline is the most widely studied choline agent precursor throughout the world, and is widely prescribed in Europe and Japan and recently became available in the United States as a dietary health supplement.

Biochemistry & Pharmacokinetics

Grouped with the B vitamins, choline is a trimethylated nitrogenous base that enters three major metabolic pathways: (1) phospholipid synthesis via phosphorylcholine; (2) acetylcholine synthesis; and (3) oxidation to betaine, which serves as a methyl donor. Endogenously, formation of Citicoline from choline is the rate-limiting step in the synthesis of phosphatidylcholine, a key membrane phospholipid. 6 Citicoline is a water-soluble compound with greater than 90% bioavailability.[8] When administered orally, it is hydrolyzed in the small intestine and almost completely absorbed as choline and cytidine, and enters the various biosynthetic pathways that utilize Citicoline as an intermediate. Citicoline thus has a sparing effect on systemic choline reserves, as well as inhibiting the breakdown of membrane phospholipids.[7] Its bioavailability is approximately the same as when administered intravenously. Once absorbed, the cytidine and choline disperse widely throughout the organism, cross the blood-brain barrier and reach the central nervous system (CNS), where they are incorporated into the phospholipid fraction of the membrane and microsomes. CDP-choline activates the biosynthesis of structural phospholipids in the neuronal membranes, increases cerebral metabolism and acts on the levels of various neurotransmitters. Thus, it has been experimentally proven that CDP-choline has a neuroprotective effect in situations of hypoxia and ischemia, as well as improved learning and memory performance in animal models of brain aging. Furthermore, it has been demonstrated that CDP-choline restores the activity of mitochondrial ATPase, of membranal Na+ /K+ ATPase, inhibits the activation of phospholipase A2, and accelerates the reabsorption of cerebral edema in various experimental models.[1] Pharmacokinetic studies using 14C Citicoline show Citicoline elimination occurs in two phases mirroring the biphasic plasma peaks, mainly via respiratory CO2 and urinary excretion. The initial peak I plasma concentration is followed by a sharp decline, which then slows over the next 4-10 hours. In the second phase, an initially rapid decline after the 24-hour plasma peak is similarly followed by a slower elimination rate. The elimination half-life is 56 hours for CO2 and 71 hours for urinary excretion.[9]

Citicoline is produced from choline chloride and orotic acid by an enzymatic process. Freebase citicoline is the form marketed as a dietary supplement in the United States. The “Jarrow Formulas, Inc.” Company markets citicoline as, “a naturally occurring, water soluble biological compound that is an essential intermediate for the synthesis of phosphatidylcholine, a major constituent for the grey matter of brain tissue (30%).” In Europe and Japan, the sodium salt of citicoline, CDP-Choline has been used in the IV form in four human clinical trials, and is approved as a drug for use in stroke, head trauma, and other neurological disorders.[5]

Side Effects/Toxicity

Citicoline has an excellent track record of clinical safety and exhibits a very low toxicity profile in humans. In a short-term, placebo-controlled, crossover study, 12 healthy adults took citicoline at daily doses of 600 and 1,000 mg or placebo for consecutive five-day periods. Transient headaches occurred in four subjects on the 600-mg dose, five on the 1,000-mg dose, and one on placebo. No changes or abnormalities were observed in hematologic clinical biochemistry, or neurological tests.[49]

A large drug surveillance study analyzed the results of citicoline treatment in 2,817 patients ages 60- 80 suffering from senility and cerebral vascular insufficiency. A total of 151 incidents of side effects were recorded, representing five percent of the patient sample. The most common adverse effects were transient in nature and included stomach pain and diarrhea in 102 cases. Vascular symptoms of hypotension, tachycardia, or bradycardia occurred in 16 cases.[50] The [LD.sub.50] of a single intravenous dose of citicoline is 4,600 mg/kg and 4,150 mg/kg in mice and rats, respectively. An oral [LD.sub.50] could not be determined as no deaths occurred at the maximum possible oral dose.[51]

No toxic effects were observed in 30-day subacute toxicity studies of oral citicoline to two groups of rats at doses of 100 mg/kg and 150 mg/kg. No changes occurred in blood chemistry, organ histology, or urinary parameters.[52]

Dosages

Clinical studies reviewed indicate the most efficacious oral dosages for citicoline range from 500- 2,000 mg daily and the IV and IM formulations have used similar ranges. Unfortunately, there was very little variation in the dosing regimens, most were either given once, twice or three times per day which may be acceptable in all studies except for the stroke related events, which are time dependent, as we know from our studies on tissue plasminogen activator (tPA).

Review of the Literature

As previously formatted in the Alternative Medicine Review Monograph of Citicoline,[5] this literature review will also encompass both the various mechanisms of action of citicoline, as well as provide a review of the studies addressing several relevant, neurological conditions and their respective clinical applications. The primary concentration will be on stroke (mainly ischemic), as it has been the focus of most of the significant clinical studies and human trials. The secondary focus will be a cursory review of other neurological conditions and related syndromes.

Mechanisms of Action Phospholipid Precursor

Evidence of Citicoline's role as a phosphatidyl-choline precursor has been found in animal studies.[10] The brain uses choline preferentially for acetylcholine synthesis, which can limit the amount of choline available for phosphatidylcholine production. When the demand for acetylcholine increases or choline stores in the brain are low, phospholipids in the neuronal membrane can be catabolized to supply the needed choline.8 Exogenous Citicoline thus helps preserve the structural and functional integrity of the neuronal membrane.[5] In an *in vitro* study, Citicoline at high concentrations stimulated brain acetylcholinesterase (AChE) along with Na+/K+-ATPase.11 The postulated mechanism involves bioconversion of Citicoline to phosphatidylcholine.[5]

Neuronal Membrane Repair

Citicoline has been investigated as a therapy for stoke patients. Three mechanisms are postulated: (1) repair of neuronal membranes via increased synthesis of phosphatidylcholine; (2) repair of damaged cholinergic neurons via potentiation of acetylcholine production; and (3) reduction of free fatty acid buildup at the site of stroke-induced nerve damage.[8]

In addition to phosphatidylcholine, Citicoline serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component. Citicoline has shown the potential to restore post-ischemic sphingomyelin levels.[12]

Citicoline also restores levels of cardiolipin, a phospholipid component of the inner mitochondrial membrane. The mechanism for this unknown, but data suggest Citicoline inhibits enzymatic hydrolysis of cardiolipin by phospholipase A2.[13] In an animal study, Citicoline decreased the formation of hydroxyl radicals following ischemia and perfusion, again suggesting Citicoline acts to decrease phospholipase stimulation.[14]

Effects on beta-Amyloid

Evidence has surfaced that Citicoline counteracts the deposition of beta-amyloid, a neurotoxic protein believed to play a central role in the pathophysiology of Alzheimer's disease (AD). The characteristic lesion in AD is the formation of plaques and neurofibrillary tangles in the hippocampus. The degree of cognitive dysfunction and neurodegeneration in AD is proportional to the buildup of beta-Amyloid protein. The number of apoptotic cells was also reduced. Memory retention as measured by a passive-avoidance learning task improved in the rats.[55]

Effects on Neurotransmitters

Evidence of citicoline's ability to enhance Norepinephrine release in humans was found in a study showing Citicoline raised urinary levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite.[15]

Citicoline increased brain levels of neurotransmitters in rats at a dose of 100mg/kg, administered daily for seven days. Norepinephrine increased in the cerebral cortex and hypothalamus, dopamine increased in the corpus striatum, and serotonin increased in the cerebral cortex, striatum, and hypothalamus.16 Rat studies have found evidence that citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine.[17]

Clinical Indications Post-stroke Rehabilitation

Several animal studies have shown a possible mechanism for citicoline's affect in stroke. Phosphatidylserine synthesis appears to be impaired after brain ischemia and Citicoline can increase levels of phosphatidylcholine by enhancing the rate-limiting enzyme in its synthesis.[18] *In vitro* evidence also suggests Citicoline provides neuroprotection after ischemia by decreasing brain levels of glutamate and increasing ATP levels.[19]

Ischemic Stroke

Stroke is the third leading cause of death in the United States and the most common cause of all adult disability. Ischemic stroke account for approximately 85% of all strokes and occurs when a cerebral vessel occludes, obstructing blood flow to a portion of the brain. The only currently approved medical stroke therapy, tissue plasminogen activator (tPA), is a thrombolytic that targets the thrombus within the blood

vessel.[20] Neuroprotective agents, another approach to stroke treatment, have generated as much interest as thrombolytic therapies.[23]

Using various mechanisms, neuroprotective agents attempt to save ischemic neurons in the brain from irreversible injury.[21] Studies in animals indicate a period of at least 4 hours after onset of complete ischemia in which many potentially viable neurons exist in the ischemic penumbra.

In humans, the ischemia may be less complete, and the time window may be longer, but human patients also tend to be older with comorbidities that may limit benefit. As many neuroprotective drugs reduce ischemic damage in animal models of stroke, this line of pharmaceutical research holds great promise. Many are searching for a safe agent that can limit ischemic damage in human stroke.

One action of neuroprotective agents limits acute injury to neurons in the penumbra region or rim of the infarct after ischemia. Neurons in the penumbra are less likely to suffer irreversible injury at early time points than are neurons in the infarct core. Many of these agents modulate neuronal receptors to reduce release of excitatory neurotransmitters, which contribute to early neuronal injury.

Other neuroprotective agents prevent potentially detrimental events associated with return of blood flow. Although return of blood flow to ischemic injury via reduction in free radical formation, the brain is generally associated with improved outcome, reperfusion may contribute to additional brain injury.[22] Returning blood contains leukocytes that may occlude small vessels and release toxic products.[23] This review will address citicoline's mechanism of action in providing membrane stabilization.

A meta-Analysis of US Clinical Trials

A positive meta-Analysis study on citicoline led by Dr. Antoni Davalos of the Hospital Universitari Doctor Josep Tructa in Spain conducted an individualized pooling data meta-analysis of all prospective, randomized, placebo-controlled, double-blind clinical trials involving the use of citicoline in the management of acute ischemic stroke. The study, presented at the 2001 annual meeting of the American Neurological Association and published in late 2002 in Stroke, pointed out that citicoline is the "only putative neuroprotectant that has shown partial positive results" in all randomized, double-blind individual trials. In addition, it is the only neuroprotective agent that has shown "efficacy in the predefined primary end point of a meta-analysis." The primary end goal was to assess the effect of citicoline on the recovery of moderate to severe acute ischemic stroke patients after three months. Efficacy was assessed using the global estimation effect (Odds Ratio) on NIHSS, mRS, and Barthel Index. Secondarily, the study looked at the efficacy of the drug in individual scales. Lastly, the issue was assessed using reports of adverse events in each trial.

Four clinical trials satisfied the predetermined requirements (must be placebo-controlled, randomized trial with more than 10 patients in each treatment group; identical end points obtained using mRS, Barthel Index, and National Institutes of Health Stroke Scale; six weeks of treatment; and must use good clinical practice). The patients were divided into four groups (placebo, 500 mg, 1,000 mg, and 2,000 mg citicoline) with 1,372 patients fulfilling the inclusion criteria (placebo = 583; citicoline = 789). The authors said, "Citicoline was associated with significantly greater recovery" by the third month. For the primary objective, citicoline increased the odds of favorable outcome or recovery by 33 percent (95 percent Cl, p = 0.0034). The most favorable dose was 2,000 mg having increased odds of recovery by 38 percent.

Individual scales produced similar results with citicoline increasing the probability of complete recovery of activities of daily living (Barthel Index) by 29 percent, complete functional recovery by 42 percent, and complete neurological recovery (NIHSS) by 28 percent.

Citicoline had no effect on mortality after three months (citicoline = 18.8 percent; placebo = 17.8 percent). There was little difference between the two groups in terms of overall adverse events. A significant difference was found specific adverse events: anxiety (citicoline = 10.5 percent, placebo = 14). In contrast with other drugs studied for stroke, which have failed in the first six hours of stroke, citicoline has shown improvement within the first 24 hours, a longer therapeutic window, the authors observed. It did not cause adverse events that led to the failure of other drugs, providing for a favorable risk-to-benefit ration for stroke patients, they added.[22,24,26]

The study concluded that treatment with oral citicoline, within the first 24 hours after symptom onset in patients with moderate to severe stroke, increases the probability of complete recovery in three months.

Meta-Analysis Review

In review of the study, I feel several points may need to be considered in future trials:
1) Patients were admitted into the clinical studies up to 24 hrs. after onset of symptoms, a much longer time frame than is used in most clinical trials; 2) a time-dose interval criteria should be considered as well to better define optimal dosing efficacy; 3) the percentage of citicoline that is incorporated into the brain; all clinical trials outside the US used IV administration at various concentrations and dosages (750 mg per day, 250 mg three times a day, and 1,000 mg per day) in contrast to the oral route used in US trials which utilized 500 and 2,000 mg per day, respectively; 4) most authors report the bioavailability is the same between oral and IV methods, but this conclusion was apparently based on absorption and excretion, not delivery of citicoline to the brain;[28] 5) finally, it may be necessary to consider combining citicoline with another agent targeted to a different pathway due to the multiple mechanisms contributing to ischemic brain injury as well those targeted to enhance post-stroke recovery.

Another trial assessed infarct size on magnetic resonance imaging (MRI) in patients with mild, moderate, and severe strokes.26 Although this study failed to show a significant difference between treated and untreated groups, there was a trend toward smaller infarct volumes in treated patients. Currently, a large international trial, the International Citicoline Trial on acUte Stroke (ICTUS), is enrolling patients within 24 hours of stroke onset. (ICTUS) is a multicenter, prospective, randomized, double-blind, placebo-controlled study whose enrollment began November 2006. As of August 2009, 1099 are enrolled at (27) active centers in Spain, (8) in Portugal, and (10) in Germany. The study will follow a sequential analysis, with the first approach to test the efficacy with 1000 patients. The upper limit has been established in 2,600 patients. The Inclusion Criteria is stroke patients with a measurable focal neurological deficit lasting for a minimum of 60 minutes; baseline NIHSS score ≥ 8, with a neuro image compatible with the diagnosis of acute ischemic stroke and symptoms referable to MCA territory and pre-stroke mRS ≤ 1. Patients will be randomized in a 1:1 ratio to receive either citicoline or placebo. Citicoline forms: 1000 mg ampoules (4 cc) and 500 mg tablets. Daily dosage: 1000 mg/12 h I.V. during the first three days and orally from the fourth day until the end of the 6 weeks treatment period. The primary outcome will be measured upon recovery at 3 months and will be evaluated using a primary end-point incorporating three components: neurological (NIHSS) ≤ 1), disability (MRS ≤ 1), and activities of daily life (BI ≥ 95), averaged using GEE.

Hemorrhagic Stroke

Citicoline has also been assessed in a double-blind, placebo-controlled pilot trial of 38 patients with intracerebral hemorrhage.[29] Patients were given 1,000 mg citicoline or placebo every 12 hours for two weeks via continuous I.V. infusion or orally if the patient was able to swallow. No differences in adverse events were reported in the citicoline group compared to placebo. Efficacy was determined after three months and was based on the number of patients who regained independence measured by modified Rankin Score.

Five patients in the citicoline group and one patient in the placebo group achieved independence (odds ratio (OR) =5.38; 95% confidence interval (CL) =0.55-52.4). The conclusion was that the drug was safe and showed trends toward efficacy.[29]

In review of the study, there remains the same issues I previously addressed in the ischemic stroke review; chiefly the potential brain bioavailability difference between the IV and oral formulations as well as the dosing intervals. In addition, the population size in this study was extremely small. Finally, standardization of ranges in ancillary factors such as blood pressure as well as the size and location of the hemorrhage should also have been used as a criteria or at least a reference point. This is important as different areas of the brain with an ischemic penumbra and infarction display differences in their historical rehabilitation characteristics.

Cognitive Dysfunction

The course of mild cognitive impairment (MCI) in the elderly involves a slight loss of memory without any significant effects on other cognitive functions. Around 12% of these patients advance annually toward Alzheimer's disease. In these patients, the cause can be due to decreased neurotransmitter formation, poor circulation (vascular dementia), or other comorbidities. Citicoline's effectiveness appears to depend on the cause of the impairment.

Several trials have been conducted on patients with mild-to-moderate memory loss30,31 as well as a double-blind trial of 95 healthy volunteers ages 50-85.[32]

In one of the studies,[30] the results showed acquisition efficiency improved. Because acquisition efficiency is specifically related to attention, the researchers postulated this finding, evidenced a dopaminergic stimulation, and improvement in attention-related cognitive mechanism. Improvements in global memory efficiency were also observed.

A recent meta-analysis of data from 12 published, double-blind, randomized human trials on citicoline and cognitive impairment in patients with chronic cerebral disorders concluded that citicoline modestly improves memory and behavior outcomes.[33]

Alzheimer's Disease

Citicoline, choline bitartrate, phosphatidylcholine (lecithin), and choline alfoscerate have all been research for dementia. Several studies targeting Alzheimer's utilizing citicoline and choline alfoscerate have demonstrated a capacity of the drugs to improve cognitive performance in early- onset Alzheimer's disease (EOAD).[30,31] A recent, multi-center, double-blind, randomized, placebo controlled trial of 261 patients for 180 days, half given choline alfoscerate 400mg three times per day, found statistically significant differences between treatments after 90 and 180 days in ADAS- Cog, MMSE, GDS, ADAS-Total, and CGI scores and after 180 days of treatment in ADAS-Behav and GIS scores. Their conclusion was that the results suggest the

clinical usefulness and tolerability of choline alfoscerate in the treatment of the cognitive symptoms of dementia disorders of the Alzheimer's type.

In review of the study, it should be noted that within the enrolled groups women out numbered men by > 3:1 in both groups. In addition, the dosing regimens were one-dimensional. Furthermore, I might suggest that for further trials an evaluation of the memory process opposed to memory scores are undertaken which may provide more direct insight into the drug's potential utility once its mechanism of action(s) is more fully understood.

Brain Neuroimaging

A study published just last year, in NMR IN BIOMEDICINE, but unrelated to Alzheimer's disease used magnetic resonance spectroscopy (MRS) to characterize the effects of citicoline on high- energy phosphate metabolites and constituents of membrane synthesis in the frontal lobe. Phosphorus (31P) metabolite data were acquired using a three-dimensional chemical-shift imaging (3D-CSI) protocol at 4 Tesla from sixteen healthy men and women (aged 47.3 ± 5.4 years) who orally self-administered 500 mg or 2000 mg of Cognizin® Citicoline (Kyowa Hakko Kogyo Co., Ltd., JAPAN) for six weeks. Individual 31P metabolites were quantified in the frontal lobe (anterior cingulate cortex, ACC) and a comparison region (parieto-occipital cortex, POC). Significant increases in phosphocreatine (PCr, +7%), beta nucleoside triphosphates (β-NTP; largely ATP in brain, +14%) and the ratio of PCr to inorganic phosphate (Pi, +32%), as well as significant changes in membrane phospholipids, were observed in the ACC after six weeks of citicoline treatment. These treatment-related alterations in phosphorus metabolites were not only regionally specific, but also tended to be of greater magnitude in subjects who received the lower dose. These data demonstrate that citicoline improves frontal lobe bioenergetics and alters phospholipid membrane turnover.

Citicoline supplementation may therefore help mitigate cognitive declines associated with aging by increasing energy reserves and utilization, as well as increasing the amount of essential phospholipid membrane components needed to synthesize and maintain cell membranes. [54]

Central Nervous System (CNS) Injury (Brain Trauma)

Citicoline facilitates memory rehabilitation in brain trauma patients by restoring blood flow to the lesion site.[34] In a single-blind, randomized trial, 216 head injury patients were assigned to two treatment groups: one received conventional treatment, while the other received conventional treatment plus 1,000 mg I.V. citicoline daily. The proportion of patients showing improvements in cognitive and motor symptoms was greater in the citicoline group; there were no differences in death rate between the two groups.[5,35]

Spinal Cord Injury

The effects of citicoline have been tested in experimental models of spinal cord injury. When 300 mg/ kg citicoline was administered to rats intraperitoneally five minutes after induction of trauma, motor function was statistically significantly better 24 and 48 hours post-trauma in the citicoline group compared to placebo.[36] In another animal study, citicoline was found to be as effective as methylprednisolone (an approved treatment for spinal cord injury) in enhancing neurological recovery after spinal cord injury.[5,37]

Parkinson's disease

Because, as previously mentioned in other study results that citicoline appears to exert a dopaminergic effect, a double-blind crossover trial was conducted on Parkinson's disease patients undergoing treatment

with L-dopa plus a decarboxylase inhibitor. Improvements in bradykinesia and rigidity were seen in subjects administered 500 mg citicoline daily via intramuscular (I.M.) injection compared to placebo; tremor was unchanged.[38]

In review of this study, it is difficult to objectively determine how the citicoline impacts the improvement in bradykinesia because there is no way to measure the amount of dopamine in the brain, the degree of substantia nigra degradation or correlation of the drug to dopamine receptor activity or whether it exerts an affect as a (COMT) or (MAO) inhibitor mechanism.

Huntington's Disease

Huntington's disease (HD) is characterized by increased brain excitotoxicity and deranged metabolism. Because citicoline appears to address these issues--mitigating excitotoxicity by decreasing brain glutamate levels and enhancing ATP19--it was tested in an experimental model of HD. Citicoline failed to provide protection from neurotoxins used in this study to simulate HD.[39]

In review of the study, I feel that the lack of dosing variability poses a significant limitation in the validity of the study. I base this observation on the fact that a sizable degree of decision making in my own decision on what dose of the various Anti-epileptic drugs (AEDs) to use for patients with epilepsy, is based, I part, upon current serum levels. In addition, we know that most of our existing AED's mechanism of action are based upon manipulation of various electrolyte channels and membrane de-sensitization mechanics to prevent not only onset, but also propagation of epileptic discharges.

Eye Conditions: Glaucoma, Amblyopia

Glaucoma, a leading cause of blindness in the elderly, is a neurodegenerative disease characterized by apoptosis of retinal ganglion cells. Damage to the retina may occur before detectable vision loss.40 In a one-year, double-blind, placebo-controlled trial, 1,000 mg I.M. citicoline daily (in two-month sessions, followed by four-month washout periods) improved retinal and visual function in 25 of 40 open-angle glaucoma patients (the other 15 received placebo).[41] These same researchers conducted a study with similar design in 30 patients with open-angle glaucoma. The study was extended for eight years and the 15 of 30 patients receiving citicoline were treated for a total of 16 two-month periods during those eight years. Citicoline significantly improved visual- evoked potentials and electroretinograms in the citicoline group compared to placebo and baseline.[42]

In an open clinical trial, 1,000 mg oral citicoline for two weeks, followed by a two-week washout and an additional two weeks of treatment, improved nerve function (measured by improved amplitude and visual-evoked potentials) in 62 percent of 21 glaucomatous eyes.[43]

It is postulated that dopaminergic stimulation is a major mechanism for citicoline's effect on the retina.[44] This hypothesis is bolstered by a recent animal study showing citicoline raises the retinal dopamine concentration in rabbits.[45] Citicoline has demonstrated retinal ganglionic cell regeneration in tissue culture.[46] Citicoline (1,000 mg I.M. daily) was found to significantly improve visual acuity in patients with Amblyopia.[5,47,48]

Discussion

Cytidine-5-diphosphocholine (CDP-choline, citicoline) is an endogenous nucleoside involved in the generation of phospholipids, membrane formation and its repair. It has been used extensively for the promotion of optimal neural and cognitive function. The many years of use have caused an evolution in dosage, method of administration and selection of patients to which citicoline was given. Initially small and conducted outside of the United States, the design of clinical trials and studies, including the length of observation, severity of disease and methodology of evaluation or the results have evolved exponentially, garnering citicoline world-wide recognition and exposure. It demonstrates beneficial effects in certain central nervous system injury models, including cerebral ischemia, neurodegenerative disorders, spinal injury and seems to enhance brain function and neural performance. When administered orally, it is readily absorbed, and its bioavailability is potentially enhanced when administered intravenously. Once absorbed, the cytidine and choline disperse widely throughout the organism, cross the blood-brain barrier and reach the central nervous system (CNS), where they are incorporated into the phospholipid fraction of the membrane and microsomes. Citicoline activates the biosynthesis of structural phospholipids in the neuronal membranes, increases cerebral metabolism and acts on the levels of various neurotransmitters. Thus, it has been experimentally proven that citicoline increases noradrenalin and dopamine levels in the CNS. Due to these pharmacological activities, citicoline has a neuroprotective effect in situations of hypoxia and ischemia, as well as improved learning and memory performance in animal models of brain aging. Furthermore, it has been demonstrated that citicoline restores the activity of mitochondrial ATPase and of membranal Na+/K+ ATPase, inhibits the activation of phospholipase A2 and accelerates the reabsorption of cerebral edema in various experimental models. Citicoline is a safe drug, as toxicological tests have shown; it has no serious effects on the cholinergic system and it is well tolerated. These pharmacological characteristics, combined with citicoline mechanisms of action, suggest that this drug may be suitable for the treatment of cerebral vascular disease, head trauma of varying severity and cognitive disorders of diverse etiology. In studies carried out on the treatment of patients with head trauma, citicoline accelerated the recovery from post-traumatic coma and the recuperation of walking ability, achieved a better final functional result and reduced the hospital stay of these patients, in addition to improving the cognitive and memory disturbances which are observed after a head trauma of lesser severity and which constitute the disorder known as post-concussion syndrome. In the treatment of patients with acute cerebral vascular disease of the ischemic type, citicoline accelerated the recovery of consciousness and motor deficit, attaining a better final result and facilitating the rehabilitation of these patients. The other important use for citicoline is in the treatment of senile cognitive impairment, which is secondary to degenerative diseases (e.g., Alzheimer's disease) and to chronic cerebral vascular disease. In patients with chronic cerebral ischemia, citicoline improves scores on cognitive evaluation scales, while in patients with senile dementia of the Alzheimer's type; it slows the disease's evolution. Beneficial neuroendocrine, neuroimmunomodulatory and neurophysiological effects have also been described. Citicoline has also been shown to be effective as co-therapy with L-Dopa for Parkinson's disease. No serious side effects have been found in any of the groups of patients treated with citicoline, which demonstrates the safety of the treatment. Because of Citicoline’s multiple and unique mechanisms of action, limitations still exist that limit our ability to measure directly (intracerebral) serum levels as well as its direct impact on other neuroprotective and neuro-restorative agents and structures. The most promising tool on the horizon is the use of modern neuroimaging. Currently, clinical trials are underway and will provide more definitive information regarding the mechanistic and clinical effects of this promising neurotherapeutic agent.

Future Direction

Animal Studies and human clinical trials need to continue to evolve. In animal studies, preclinical testing of neuroprotective candidates should be standardized. Conventional stroke models should be updated to utilize older animals with common comorbidities such as atherosclerosis. Finally, combination therapies need to be tried.

In human trials, the effects of neuroprotective agents on infarct size have been time dependent, and treatment has often been initiated much later than in successful experimental stroke models. Insufficient doses, different formulations, and their respective bioavailability at the target areas may be other considerations to address. Next, we need to continue striving for larger sample sizes in trials and more standardization of baseline variables. Lastly, citicoline in respect to its use in ischemic injury and repair therapies need to be considered in conjunction with reperfusion agents such as tPA as well as concurrent application with cerebral plasticity stimulation (trophic factors) and cell therapy interventions.

Conclusion

Acute stroke is a leading cause of morbidity and mortality worldwide. Like stroke, the effects on the lives of patients, caregivers and society as a whole for other neurological conditions such as Parkinson's, Alzheimer's, traumatic brain injury and cognitive disorders, impose an enormous economic burden. Unfortunately, our treatments have thus far been less than satisfactory. Neuroprotection and neurorepair has been elusive goals to this point in clinical medicine. Citicoline is the most widely studied choline precursor in the world. Researches in both animal experiments and human clinical trials have provided evidence of its cholinergic and neuroprotective actions. As a dietary supplement, citicoline appears to be beneficial for improving the integrity and functionality of the nerve cell membranes that are involved in membrane repair. Clinical studies indicate that citicoline appears to improve cognitive, neurological and visual function. Its safety profile has been shown to be safe for long-term clinical use and consumption as a dietary supplement.

In a commentary regarding the recently completed neuroimaging, study involving Cognizin ® Citicoline out of McLean Hospital, an affiliate of Harvard Medical School, Dr. Perry Renshaw, M.D., PhD. Director of Magnetic Resonance Imaging, The Brain Institute of the University of Utah, sums up this conclusion rather eloquently and succinctly: "This most recent study confirms previous research and bolsters our conviction that citicoline, taken at a minimum dosage of 500 mg each day, is a simple and natural nutrient for your brain that may help you feel better, think more clearly, sleep better, increase your memory and improve your overall quality of life."

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    1Cognitive Neuroimaging Laboratory and 2Brain Imaging Center, McLean Hospital, Belmont, MA, and 3Department of Psychiatry, Harvard Medical School, Boston,
56. MA, USA; 4Healthcare Products Development Center, Kyowa Hakko Kogyo Co., Ltd., Tsukuba, Ibaraki, JAPAN
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