Therapeutic Applications of Citicoline for Stroke and Cognitive Dysfunction in the Elderly: A Review of the Literature

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Abstract
Citicoline (CDP-choline; cytidine 5’-diphosphocholine), a form of the essential nutrient choline, shows promise of clinical efficacy in elderly patients with cognitive deficits, inefficient memory, and early-stage Alzheimer’s disease. Citicoline has also been investigated as a therapy in stroke patients, although the results of trials to date are inconclusive. Produced endogenously, citicoline serves as a choline donor in the metabolic pathways for biosynthesis of acetylcholine and neuronal membrane phospholipids, chiefly phosphatidylcholine. The principal components of citicoline, choline and cytidine, are readily absorbed in the GI tract and easily cross the blood-brain barrier. Exogenous citicoline, as the sodium salt, has been researched in animal experiments and human clinical trials that provide 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. This review, while not intended to be exhaustive, highlights the published, peer-reviewed research on citicoline with brief discussions on toxicology and safety, mechanisms of action, and pharmacokinetics.


Introduction
Citicoline is a complex organic molecule (Figure 1) that functions as an intermediate in the biosynthesis of cell membrane phospholipids. Citicoline is also known as CDP-choline and cytidine diphosphate choline (cytidine 5’-diphosphocholine). CDP-choline belongs to the group of biomolecules in living systems known as “nucleotides” that play important roles in cellular metabolism. The basic structure of a nucleotide contains ribose with a nitrogenous base and a phosphate group. CDP-choline is composed of ribose, pyrophosphate, cytosine (a nitrogenous base), and choline.1

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 is the rate-limiting step in the synthesis of phosphatidylcholine, a key membrane

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phospholipid, from choline. Exogenous citicoline, which is hydrolyzed in the small intestine and readily absorbed as choline and cytidine, 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.2

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 and as a drug in Japan. The sodium salt of citicoline, the form used in clinical trials, is sold as a drug in Europe.

**Pharmacokinetics and Metabolism**

Citicoline is a water-soluble compound with greater than 90-percent bioavailability.3 Pharmacokinetic studies on healthy adults have shown oral doses of citicoline are rapidly absorbed, with less than one percent excreted in feces. Plasma levels peak in a biphasic manner, at one hour after ingestion followed by a second larger peak at 24 hours post-dosing. Citicoline is metabolized in the gut wall and liver. The byproducts of exogenous citicoline formed by hydrolysis in the intestinal wall are choline and cytidine. Following absorption, choline and cytidine are dispersed throughout the body, enter systemic circulation for utilization in various biosynthetic pathways, and cross the blood-brain barrier for re-synthesis into citicoline in the brain.4

Pharmacokinetic studies using 14C citicoline show citicoline elimination occurs mainly via respiratory CO₂ and urinary excretion, in two phases mirroring the biphasic plasma peaks. The initial peak in 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.5

Endogenous citicoline serves as an intermediate in the biosynthesis of phospholipids, including phosphatidylcholine, the primary phospholipid in cell membranes.6 Cytidine, a major component of RNA, undergoes cytoplasmic conversion to cytidine triphosphate (CTP). In the citicoline metabolic pathway, choline is phosphorylated by the enzyme choline kinase; the resulting phosphorylcholine combines with CTP to form citicoline.7 Citicoline then combines with diacylglycerol (DAG), forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction.3

Oral administration of citicoline raises plasma levels of cytidine and choline in rats within
six to eight hours. Prolonged administration for 42 and 90 days increases brain concentrations of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine – the three major phospholipids in brain cell membranes. Evidence for the role of these metabolites as substrates for phosphatidylcholine synthesis was found in a study giving rats daily oral doses of citicoline for 90 days. At a dose of 500 mg/kg per day phosphatidylcholine levels increased by 25 percent, phosphatidylethanolamine by 17 percent, and phosphatidylserine by 42 percent.8

Administration of citicoline to aged rats activates CTP:phosphocholine cytidylyltransferase, the rate-limiting enzyme in the citicoline pathway of phosphatidylcholine synthesis in the brain cell membrane.9 Choline and cytidine are the major metabolites released via hydrolysis of citicoline during absorption.

A single oral dose of citicoline raises plasma choline levels in both younger and older subjects. Using protein magnetic resonance spectroscopy, it was found that brain choline levels in older subjects decreased after citicoline administration, but increased in younger subjects. The postulated explanation is that the cytidine moiety of citicoline may be taken up by brain cells in older adults more rapidly than choline. Based on this finding, it is suggested that cytidine is the citicoline component primarily responsible for stimulating phosphatidylcholine synthesis in older subjects.10 Using protein-decoupled phosphorus magnetic resonance spectroscopy, it has been shown that citicoline administration to older subjects for six weeks increases brain levels of phosphodiester, byproducts of phospholipid metabolism. This is seen as evidence that citicoline increases phospholipid synthesis and turnover, which may help reverse cognitive functional deficits associated with aging.11

In clinical trials, citicoline has been administered orally and by intramuscular injection.

Mechanisms of Action

Phospholipid Precursor

The pharmacological action of citicoline appears to involve mechanisms that extend beyond phospholipid metabolism. Citicoline metabolites – choline, methionine, betaine, and cytidine-derived nucleotides – enter a number of metabolic pathways. Evidence of citicoline’s role as a phosphatidylcholine precursor has been found in animal studies.12

Biochemical markers of cholinergic nerve transmission are known to be deficient in conditions characterized by degeneration of cholinergic neurons, such as Alzheimer’s disease (AD). Citicoline modestly improves cognitive function in AD by serving as an acetylcholine precursor.13 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 may be catabolized to supply the needed choline.3 Exogenous citicoline may thus help preserve the structural and functional integrity of the neuronal membrane.

In an in vitro study, citicoline at high concentrations stimulated brain acetylcholinesterase (AChE), along with Na+/K+-ATPase.14 The postulated mechanism involves bioconversion of citicoline to phosphatidylcholine in the external leaflet of the neuronal membrane, the site of AChE activity. Citicoline is not known to function as an AChE inhibitor in humans, however. Thus, the significance of this finding with regard to citicoline’s therapeutic mechanisms in cognitive disorders is unknown.

Neuronal Membrane Repair

Citicoline has been investigated as a therapy for stroke patients. Three mechanisms are postulated: (1) repair of the neuronal membrane 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.³

Citicoline protects cholinergic neurons from autocannibalism, a process in which membrane phospholipids are catabolized to provide choline for synthesis of acetylcholine. This occurs when choline supplies are depleted, necessitating sacrifice of membrane phospholipids to maintain neurotransmission. As an exogenous source of choline for acetylcholine production, citicoline thus spares membrane phospholipids (in particular, phosphatidylcholine) and prevents neuronal cell death.¹⁵

In addition to phosphatidylcholine, citicoline serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component. Citicoline has shown ability to restore post-ischemic sphingomyelin levels.¹⁶ Sphingomyelin is formed from ceramide, a lipid synthesized in the endoplasmic reticulum that appears to function as an intracellular second messenger and is a byproduct of an intramembranal reaction between ceramide and phosphatidylcholine.¹⁷

Citicoline also restores levels of cardiolipin, a phospholipid component of the inner mitochondrial membrane. The mechanism for this is unknown, but data suggest citicoline inhibits enzymatic hydrolysis of cardiolipin by phospholipase A₂. Citicoline inhibits release of arachidonic acid, which serves as substrate for phospholipase A₁. The arachidonic acid content of phosphatidylcholine is decreased following post-ischemic reperfusion due to hydrolysis of the phospholipid. Because citicoline replenishes the arachidonic acid content of phosphatidylcholine, it is suggested that citicoline prevents activation of phospholipase A₂, rather than inhibiting its activity.¹⁸ Recent investigative work has shown citicoline is not an in vivo phospholipase A₂ inhibitor. In an animal study, citicoline was found to decrease the formation of hydroxyl radicals following ischemia and perfusion, again suggesting citicoline acts to decrease phospholipase stimulation.¹⁹

Citicoline’s effect on phospholipase A₂ may account for the observation that citicoline restores sphingomyelin levels after ischemia/reperfusion, protecting hippocampal neurons in the process.¹⁵ Tumor necrosis factor, which is released during ischemia, stimulates sphingomyelinase, resulting in hydrolysis of sphingomyelin. Evidence suggests that this process is mediated by the phospholipase/arachidonic acid pathway.²⁰ Modulation of phospholipase activity by citicoline and concomitant inhibition of sphingomyelinase could be another route by which citicoline provides neuroprotection.

**Effect on beta-Amyloid**

Evidence has surfaced that citicoline may counteract the deposition of beta-amyloid, a neurotoxic protein believed to play a central role in the pathophysiology of 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.²¹,²² Citicoline counteracted neuronal degeneration in the rat hippocampus induced by intrahippocampal injection 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.²³

In an *in vitro* study showing increases in phospholipid levels of rat brain cells induced by choline plus cytidine (citicoline components), excretion of amyloid precursor protein (APP) was also stimulated. Found in the lipid bilayer of neuronal membranes, APP contains a peptide that forms amyloid deposits in Alzheimer’s patients. This follows abnormal cleavage of APP that occurs due to decreased phospholipid content (phosphatidylcholine and phosphatidylethanolamine) with resulting destabilization of the cell membrane. This formation of amyloidogenic APP fragments is an abnormal occurrence that takes place as a result of aging or neuron damage. Under normal conditions, APP is cleaved in such a way that the amyloidogenic peptide is broken down, resulting in the extracellular secretion of nonplaque-forming APP fragments. Because citicoline restores membrane phospholipids, it may thus promote this normal cleavage process. Choline plus
cytidine were found to stimulate secretion of intact, neurotrophic APP from rat brain cells. These findings suggest citicoline may promote neuronal regeneration in Alzheimer’s patients.24

**Effect on Neurotransmitters**

Citicoline increased brain levels of neurotransmitters in rats at a dose of 100 mg/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.25

An earlier study found somewhat different results. Intravenous administration of citicoline to rats increased dopamine synthesis in the corpus striatum; tyrosine levels also increased. The authors suggested citicoline may stimulate tyrosine hydroxylase activity, thus potentiating dopamine synthesis. Norepinephrine levels increased slightly in the cerebral cortex; no change was observed in the brain stem. However, serotonin levels and rate of synthesis in the midbrain and hypothalamus decreased in this study. This effect was seen with doses ranging from 10-100 mg/kg. Serotonin synthesis in the cortex was unchanged. This effect of activating dopamine while inhibiting serotonin is suggested as a mechanistic explanation for the reported anti-parkinsonism and central nervous system (CNS) stimulation by citicoline.26

Another investigation by the same research team found citicoline inhibits synaptic dopamine uptake in the corpus striatum of rats, leading the researchers to propose this as a possible explanation for the therapeutic effect of citicoline in Parkinson’s disease (see below).27 Evidence of citicoline’s ability to enhance norepinephrine release in humans was found in a study showing that citicoline raised urinary levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite.28

Rat studies have found evidence that citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine.29

**Animal Studies**

**Cerebro-protection**

Citicoline injected experimentally into the cerebrum of gerbils shortly before artificially-induced ischemia has demonstrated an ability to partially restore phosphatidylcholine levels while inhibiting free fatty acid release, suggesting stabilization of the neuronal membrane.15

In another gerbil study, citicoline restored ischemia-depleted levels of phosphatidylcholine, sphingomyelin, and cardiolipin after one day of reperfusion. In addition, this study found that after three days of reperfusion, citicoline increased both glutathione levels and glutathione reductase activity, suggesting citicoline may contribute to reduction of oxidative stress.30

Traumatic injury damages the brain in numerous ways, including cell death due to edema, disruption of the blood-brain barrier, ischemia, and shear stress. Three underlying pathologies are thought to be at work at the site of brain injury: (1) breakdown of phospholipids in the cell membrane, resulting in decreased phosphatidylcholine content; (2) release of free fatty acids from the degraded membrane, which causes local edema due to accumulation of inflammatory arachidonic acid metabolites such as prostaglandins and leukotrienes; and (3) decreased release of acetylcholine, resulting in impaired cholinergic nerve transmission.

The ability of citicoline to reverse the effects of brain injury has been tested in animal models of cerebral ischemia. Administered intraperitoneally, citicoline was found to reduce brain edema and decrease breakdown of the blood-brain barrier in rats at a dose of 400 mg/kg.31

Citicoline has been shown to delay brain cell membrane damage and behavioral dysfunction in spontaneously hypertensive rats with ischemia caused by artificially-induced occlusion of the lateral middle cerebral artery.32 This effect of citicoline was greatest in rats with mild cell injury due to lack of oxygen.

In another similar study, citicoline was tested in an animal stroke model. Temporary focal ischemia was artificially induced in rats via blockage of the right middle cerebral artery and
maintained for two hours. For the next six days the animals were treated with citicoline at doses of 100 or 500 mg/kg, or placebo. In the rats administered the higher citicoline dose, the “infarct volumes” (volume of damaged brain tissue at ischemia sites) were significantly smaller than in the placebo group. Similar reductions in the lower-dose group failed to reach statistical significance. Less brain edema was also observed in the rats given citicoline. 33

Citicoline appears to reverse neuronal membrane pathology that occurs in cerebral ischemia. Depletion of ATP causes cytidine 5’-monophosphate to accumulate within the membrane, which in turn increases bioconversion of phosphatidylcholine to diacylglycerol and free fatty acids (Figure 2). These breakdown products can become toxic to the membrane due to excess levels of free radicals, lipid peroxides, and arachidonic acid and its metabolites such as leukotrienes. The protective effect of citicoline against these pathologies was demonstrated in gerbils with artificially induced forebrain ischemia. 4 The gerbils were pretreated with either citicoline or saline as control. The animals were anesthetized, the carotid arteries clamped to induce ischemia, and then reperfused for six days. Citicoline provided partial protection against the damaging ischemic effects. Attenuated arachidonic acid release, decreased blood-brain barrier dysfunction, less edema, and protection of neurons

**Figure 2. Conversion of Diglycerides to Phosphatidylcholine or Free Fatty Acids under Various Conditions: Normal, Ischemia, and Exogenous Citicoline**

A. Normal

<table>
<thead>
<tr>
<th>Diglycerides + CDP-choline</th>
<th>Phosphatidylcholine + Monoglycerides</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Free Fatty Acids</td>
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B. Ischemia

<table>
<thead>
<tr>
<th>Diglycerides + CDP-choline</th>
<th>Phosphatidylcholine + Monoglycerides</th>
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<tbody>
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<td></td>
<td>Free Fatty Acids</td>
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C. Citicoline Treatment

<table>
<thead>
<tr>
<th>Exogenous Citicoline</th>
<th>Phosphatidylcholine + Monoglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diglycerides + Increased CDP-choline</td>
<td>Free Fatty Acids</td>
</tr>
</tbody>
</table>

From: Weiss GB. Metabolism and actions of CDP-choline as an endogenous compound and administered exogenously as citicoline. Life Sciences 1995;56:647.
in the hippocampus were observed in the citicoline-treated animals. Based on previous findings of increased free radical production in hippocampal neurons following reperfusion, it is theorized citicoline inhibits oxygen free radical production that accompanies arachidonic acid metabolism.

*In vitro* studies using neuronal cultures from chick embryos have shown that citicoline may protect the hippocampus from injury. Addition of citicoline to the cultures both before and after experimentally induced hippocampal injury resulted in a protective effect.  

### Memory and Learning

Brain aging may be associated with decreased membrane phospholipid content, leading to impaired membrane biofunction along with loss of cholinergic neurons. Memory and cognition depend on normal neuron-to-neuron communication via transmission of nerve impulses along the neuronal membrane.

In one experiment citicoline was administered intraperitoneally to aged rats with cognitive and motor impairment. Using tests of active and passive avoidance behavior, it was shown that citicoline improved learning and memory capacity. Motor performance also improved. Citicoline also improved cognitive function in rats injected with scopolamine, an amnesia-inducing anticholinergic drug, supporting the conclusion that citicoline exerts cholinergic action.  

The effects of citicoline on retention of learned behavior in rats were observed in a series of experiments. Memory deficits were artificially induced in young adult and aged rats via oxygen deprivation (hypoxia), electric shock, and administration of scopolamine. Citicoline improved memory performance in older but not younger rats, which is consistent with the notion that citicoline corrects impaired phospholipid metabolism. Citicoline prevented amnesia induced by scopolamine and by electric shock. Citicoline prevented memory impairment in rats caused by sodium nitrate-induced hypoxia. Additional experiments showed citicoline improved learning ability in rats with fetal alcohol syndrome induced by feeding alcohol to dams during pregnancy. The overall conclusion drawn from these studies is that citicoline improves memory only in animals with measurable memory deficits.

Citicoline, however, has demonstrated the ability to facilitate learning and memory in young, normal dogs. Ten one-year old dogs were put through a series of operant-conditioned-learning experiments over a 42-day period. Compared to control animals, dogs administered citicoline daily prior to repetition of these procedures exhibited superior memory processes including acquisition, retention, and retrieval.

### Citicoline as Adjunctive Therapy in an Animal Model of Embolic Stroke

Citicoline has been tested in rats as a possible adjunct to thrombolytic therapy in embolic stroke. In one experiment, embolism was artificially created in the carotid arteries of 83 Sprague-Dawley rats. The rats were then divided into six treatment groups, including a saline-treated control group, using citicoline at two different doses (250 mg/kg; 500 mg/kg) with or without the antithrombotic agent – recombinant tissue plasminogen activator (rtPA). Size of the cerebral infarction caused by an embolism was significantly reduced in the citicoline-plus-rtPA groups. Functional recovery occurred in both the rats that received citicoline plus rtPA and rats on citicoline alone at the higher dose.

In another similar experiment, citicoline, alone or in combination with the thrombolytic agent urokinase, was injected into rats following occlusion of the middle cerebral artery. This procedure causes focal ischemia and infarction in the cerebral cortex. Saline-treated rats were used as controls. Citicoline, injected as a single dose or intermittently, significantly reduced neuronal damage. Enhanced neuroprotection was seen in the rats treated with citicoline plus urokinase.
Human Clinical Trials

Stroke Therapy

Citicoline has been tested on stroke patients in controlled trials. A multicenter, double-blind, placebo-controlled trial evaluated the effect of citicoline on 272 stroke patients in the acute stage of moderate-to-severe cerebral infarction with mild-to-moderate disturbances in consciousness. In the treatment group, 133 patients received 1,000 mg citicoline by daily intravenous administration for 14 days. Compared to the remaining 139 patients on placebo, the level of consciousness improved significantly in the citicoline group. By day 14, 54 percent of patients on citicoline showed improvement, compared to 29 percent of placebo patients. The results suggest intravenous citicoline promotes recovery from reversible tissue damage in the acute stages of stroke, while mitigating the aggravation of post-stroke symptoms.

Other trials have administered citicoline to post-stroke patients, demonstrating similar results to the above study, including enhancement of recovery with improvements in parameters of neurological function, such as muscle strength, ambulation, and cognition. According to a recent analysis of these trials, initiating citicoline within the first 24 hours after stroke onset “increases the probability of complete recovery at three months.”

A multicenter, double-blind controlled trial, conducted by the Citicoline Stroke Study Group, examined the effects of oral citicoline on 259 stroke patients. Three doses of citicoline (500 mg; 1,000 mg; or 2,000 mg) were administered to three groups of 65 patients each, within 24 hours of stroke onset, while a fourth group received placebo. Treatment was continued for six weeks, with a six-week follow-up period. The primary clinical endpoint was a change in the Barthel Index of Neurological Function. The baseline NIH Stroke Scale (NIHSS) score was assessed as a second variable to decrease the effect of baseline differences in stroke severity. After 12 weeks, patients in the groups receiving 500 mg or 2,000 mg citicoline were found to have twice the chance of stroke recovery compared to patients on placebo.

Curiously, no differences were seen between the 1,000-mg citicoline group and the placebo group. No clear explanation was found for this apparent anomaly, other than a difference in patient weight in this group. Because the 2,000-mg group had a higher incidence of dizziness and accidental injury, the researchers concluded 500 mg per day might be the optimum citicoline dose.

The Citicoline Stroke Study Group subsequently conducted a second double-blind study similar to the above trial. This multicenter trial enrolled 394 patients suffering from acute ischemic stroke, randomly assigning patients to the treatment and placebo groups on a two-to-one basis. Based on the previous results, 500 mg was selected as the daily citicoline dose; the Barthel Index and NIHSS score were used to assess efficacy. No differences were found between the treatment and placebo groups after six weeks of treatment and follow-up. However, an inequality in baseline stroke severity between treatment and placebo groups was discovered; 34 percent of patients in the placebo group had had mild strokes compared to 22 percent in the treatment group. As reported, “This baseline imbalance may have impacted the overall efficacy results in this trial.”

The most recent investigative effort assessing the effect of citicoline in acute ischemic stroke was a double-blind, multicenter trial of 899 patients. The study enrolled patients with acute ischemic stroke in the region of the middle cerebral artery. The subjects received either 2,000 mg oral citicoline (1,000 mg twice daily) or placebo for six weeks. A six-week, post-treatment follow-up period then ensued. The primary study endpoint was the proportion of patients showing a seven-point or greater improvement from baseline in the NIHSS score. The outcome was virtually the same for both groups: 52 percent of patients in the citicoline group and 51 percent in the placebo group reached this level of improvement. The researchers concluded: “Citicoline was safe but ineffectivie in improving the outcome of patients with acute ischemic stroke as measured by the planned analyses.” The citicoline group did have a significantly higher proportion of patients showing improvement after six weeks, as measured by
the Barthel Index, but this disappeared at the week-12 analysis.\textsuperscript{44}

**Cognition in the Elderly**

Citicoline’s potential as a treatment for memory impairment associated with aging was studied in a 1989 double-blind trial of 84 elderly patients with mild-to-moderate memory loss.\textsuperscript{45} Based on the role of citicoline as an intermediate of phosphatidylcholine biosynthesis, it was hypothesized citicoline could reverse age-dependent histopathological changes within the brain neuronal membrane, thereby restoring memory function. The subjects, who all exhibited memory loss as assessed by scores on the Mini Mental State Examination (MMSE), took 1,000 mg citicoline daily or placebo for six weeks. The Randt Memory Test was administered after three weeks and at the end of the treatment period. In addition to memory factors such as immediate recall, delayed recall, and global memory efficiency, the Randt test measures three cognitive function parameters: encoding and organization (E-O), cognitive efficiency (CE), and acquisition efficiency (AE). The results showed AE improved while E-O and CE remained unchanged. Because AE is specifically related to attention, the researchers postulated this finding evidenced a dopaminergic effect of citicoline, based on an association between dopaminergic stimulation and improvement in attention-related cognitive mechanisms. Improvements in global memory efficiency were also observed.

The effect of citicoline on verbal memory in the elderly was tested in a double-blind trial using 95 healthy volunteers ages 50-85.\textsuperscript{46} This study took place in two phases. In the initial phase, all subjects took 1,000 mg citicoline or placebo daily for three months. Analysis of the data revealed a subgroup with relatively poor memory. These subjects were recruited for the second crossover trial phase and given either placebo or 2,000 mg citicoline daily for three months. After the initial phase, improvement with citicoline occurred only in the poor-memory subgroup, which showed gains in delayed recall and logical memory. At the end of the second phase, greater improvements occurred in the citicoline group, suggesting that 2,000 mg per day is a more effective dose for age-associated memory impairment.

In a double-blind, crossover trial, citicoline was administered orally to 24 memory-impaired elderly subjects for four weeks. Citicoline was given alone at 500 or 1,000 mg doses, or combined with nimodipine, a calcium channel blocker used to treat neurological deficits in brain hemorrhage patients (citicoline 300 mg/day plus nimodipine 90 mg/day). Pre- and post-treatment memory performance was evaluated. The results showed that citicoline improved the ability to recall words and objects after viewing them for two seconds each. In tests of recognition, where subjects attempt to identify previously viewed words and objects randomly mixed with non-viewed items, no improvement was observed. Positive results occurred in all three treatment groups.\textsuperscript{47}

A recent meta-analysis looked at data from published, double-blind, randomized human trials on citicoline and cognitive impairment in patients with chronic cerebral disorders. It was concluded that citicoline modestly improves memory and behavioral outcomes.\textsuperscript{48}

**Effect on Brain Wave Activity**

Citicoline appears to reverse abnormalities in brain electrical patterns that occur with aging. Age-related cognitive disorders are typically associated with increases in the delta, theta, and fast beta ranges, while the alpha and slow beta frequencies decrease. In an uncontrolled study, 24 patients with “organic brain syndrome” (characterized by symptoms such as disorientation, cognitive impairment, and emotional lability in patients suffering from cerebrovascular or degenerative brain disease) were administered intravenous citicoline at a dose of 500 mg daily. As measured by EEG, statistically significant increases in alpha frequencies were observed, along with decreases in delta frequencies. Insignificant reductions in theta and slow beta frequencies were also seen; clinical parameters improved.\textsuperscript{49}

In another study analyzing changes in brain mapping with citicoline administration, 19 Alzheimer’s disease patients received 100 mg oral
citicoline daily for one month. Thirteen subjects were early-onset (EOAD) Alzheimer’s patients; the remaining six were late onset (LOAD). Theta band decreases in the frontal-temporal region were observed, along with frontal decreases of beta bands. A moderate increase in the alpha frequency was noted in the occipital regions of LOAD patients. No other changes occurred in the relative power of other frequencies. Cerebral hemodynamics also improved, measured by increases in blood flow velocities. Immunological changes and slightly reduced serum cytokine levels were observed. EOAD patients, who are known to have higher histamine levels than LOAD patients, showed lowered histamine levels after one month on citicoline. 50

**Brain Injury**

Brain injury results in depletion of cell membrane phospholipids, followed by intracellular cerebral edema due to breakdown of the sodium-potassium pump. 51 In a single-blind, randomized trial, 216 head injury patients were assigned to two treatment groups. One group received conventional treatment as control while the other received conventional treatment plus intravenous citicoline at a dose of 1,000 mg 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. 52

Other studies have shown citicoline facilitates memory rehabilitation in brain trauma patients by restoring blood flow to the lesion site. 53 In a small double-blind study, one month on 1,000 mg oral citicoline daily significantly improved the ability to recall designs in patients with concussion, as compared to placebo. There were no significant differences between the two groups in other tests of cognitive function, such as word or location recall or verbal fluency. In the placebo group, a greater trend toward complaints of post-concussional symptoms such as headache, dizziness, and tinnitus was observed at follow-up. 54

**Alzheimer’s Disease**

Citicoline has demonstrated a possible ability to improve cognitive performance in EOAD. A 1994 double-blind study examined the effect of one-month treatment with citicoline on cognition in 20 Alzheimer’s patients. Following citicoline treatment (1,000 mg/day orally), cognitive function assessed using MMSE improved slightly in an EOAD patient subgroup, as shown by small, but statistically significant (p<0.005) increases in MMSE scores. MMSE scores decreased in patients in later stages of the disease. Spatial-temporal orientation improved in the total group, with a more marked difference in EOAD patients. 55

A more recent double-blind, placebo-controlled trial tested the effect of citicoline therapy on 30 patients with mild-to-moderate senile dementia of the Alzheimer’s type. Citicoline was administered over a 12-week period at a daily dose of 1,000 mg. The cognitive function subset of the Alzheimer’s Disease Assessment Scale (ADAS) and “clinical interview based impression of change” (CIBIC) were utilized as primary outcome measures, with additional subsets of the ADAS and the MMSE used as secondary measurements. The overall results showed differences between the citicoline and placebo groups, but the changes were only trends that did not reach statistical significance. Non-significant improvements were seen with citicoline in the ADAS-cognitive scores and CIBIC scores. 56

Brain hemodynamics were assessed in the above two trials. Citicoline was shown to slightly increase cerebral blood flow and velocities, in comparison with placebo. In the first trial this was postulated as resulting from immunogenic or neurotrophic mechanisms, since a direct vasoactive effect was not observed. The mechanisms are consistent with citicoline’s apparent role as a cholinergic system potentiator, via acetylcholine biosynthesis and activation of muscarinic receptors in the central nervous system. 55

Based on a hypothetical autoimmune component in the pathophysiology of AD, a study was conducted to assess citicoline’s effect on immune function in Alzheimer’s patients. Citicoline,
at an oral dose of 1,000 mg daily, was administered to three groups: EOAD patients, LOAD patients, and patients with multi-infarct dementia; a fourth group served as control. Increased levels of interleukin-1β were normalized after three months on citicoline.57

Other Therapeutic Effects

Glaucoma/Amblyopia

Results from two open trials suggest that citicoline repairs damage to the optic nerve that occurs in glaucoma.58 Citicoline appears to provide neuroprotection to the retina by enhancing phosphatidylcholine synthesis. 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.59 In a short-term, double-blind, placebo-controlled trial, citicoline administered by intramuscular injection (1,000 mg/day) improved retinal and visual function in open-angle glaucoma patients.60 It is postulated that dopaminergic stimulation is a major mechanism for citicoline’s effect on the retina.58 This hypothesis is bolstered by a recent animal study showing that citicoline raises the retinal dopamine concentration in rabbits.61

Citicoline, at a dose of 1,000 mg daily administered by intramuscular injection was found to significantly improve visual acuity in patients with amblyopia.62,63

Parkinson’s Disease

Based on citicoline’s hypothetical ability to improve dopaminergic function, a double-blind crossover trial was conducted on Parkinson’s disease patients who were undergoing treatment with L-dopa plus a decarboxylase inhibitor. Improvements in bradykinesia and rigidity were seen in subjects administered citicoline (500 mg daily via intramuscular injection) when compared to placebo subjects; tremor was unchanged.64

Vascular Dementia

A small, double-blind clinical trial found no effect of citicoline treatment in 30 patients age 55 or older with moderate-to-severe vascular dementia (VaD). This study excluded patients with AD, stroke, head injury, or other severe neurological disorders. The diagnosis of VaD was based on brain abnormalities measured by MRI, along with a battery of neuropsychological tests assessing cognitive and psychomotor function. Fifteen subjects were administered a 500 mg citicoline tablet twice daily, while 15 took placebo tablets. Outcomes were assessed after six and 12 months. No differences were found between treatment and placebo groups in neuropsychological performance at baseline and at the study end. MRIs showed exacerbation of brain pathology in both groups as the study progressed.65

Toxicology

The LD₅₀ of a single intravenous dose of citicoline was 4,600 mg/kg and 4,150 mg/kg in mice and rats, respectively. An oral LD₅₀ could not be determined as no deaths occurred at the maximum possible oral dose.66

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.67

The effect of chronic oral consumption of citicoline was studied in dogs who were fed a single 1.5 g/kg dose daily for six months. No toxic effects were seen nor did any physiological, biochemical, neurological, or morphological abnormalities occur.68

Citicoline 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 hematology, clinical biochemistry, or neurological tests.69

In an unpublished GLP acute toxicity study, free-base citicoline was administered to male and female rats at a dose of 2,000 mg/kg body weight for 14 days. No changes in body
weight, deaths, clinical symptoms or gross pathological changes were observed. A GLP, sub-acute, 90-day toxicology study on free-base citicoline is underway, with results slated for release in early 2004.

Clinical Safety

Citicoline has an excellent track record of clinical safety. 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.70

Conclusion and Future Directions

Citicoline is a form of the B-vitamin choline that serves as a choline donor and intermediate in the biosynthesis of phospholipids and acetylcholine. Citicoline reduces ischemic injury in the CNS by preserving membrane phospholipids, chiefly phosphatidylcholine. As a therapeutic intervention in acute stroke the studies have yielded mixed results. It is possible exogenous citicoline may increase the possibility of complete recovery when treatment is started within 24 hours of stroke onset. Citicoline therapy might improve cognitive function in elderly patients with memory deficits, mild cognitive impairment, and senile dementia of the Alzheimer’s type. Citicoline exhibits a very low toxicity profile, and appears to be safe for long-term clinical use and consumption as a dietary supplement. A human clinical trial is soon to begin that will assess the effect of free-base citicoline on memory in 50-75 year-olds.

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