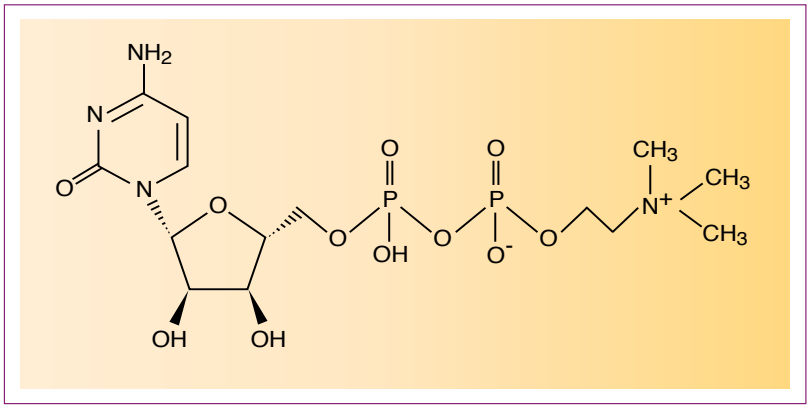
Monograph

Citicoline



Introduction

Citicoline is a complex organic molecule 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. CDP-choline is composed of ribose, pyrophosphate, cytosine (a nitrogenous base), and choline.[1] Exogenous citicoline 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. Animal and clinical studies indicate the potential of citicoline to improve cognitive deficits, stroke rehabilitation, brain and spinal cord injuries, neurological diseases, and eye conditions.

Biochemistry

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.[2] 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.[3] Citicoline then combines with diacylglycerol (DAG), forming phosphatidylcholine, with choline phosphotransferase serving as the enzyme catalyst in this reaction.[4]

Exogenous citicoline, 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.[5]

Pharmacokinetics

Citicoline is a water-soluble compound with greater than 90-percent bioavailability.[4] Pharmacokinetic studies on healthy adults show 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.[6]

Pharmacokinetic studies using ^{14}C citicoline show citicoline elimination occurs in two phases mirroring the biphasic plasma peaks, mainly via respiratory CO_2 and urinary excretion. 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 CO_2 and 71 hours for urinary excretion.[7]

Mechanisms of Action

Phospholipid Precursor

Evidence of citicoline's role as a phosphatidylcholine precursor has been found in animal studies.[8] 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.[4] Exogenous citicoline thus helps 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.[9] The postulated mechanism involves bioconversion of citicoline to phosphatidylcholine.

Neuronal Membrane Repair

Citicoline has been investigated as a therapy for stroke 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.[4]

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.[10]

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 A_2.[11] In an animal study, citicoline decreased the formation of hydroxyl radicals following ischemia and perfusion, again suggesting citicoline acts to decrease phospholipase stimulation.[12]

Effect 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.[13,14] 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.[15]

Effect 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.[16]

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.[17] Rat studies have found evidence that citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine.[18]

Clinical Indications

Post-stroke Rehabilitation

Animal studies have helped elucidate a possible mechanism for citicoline's affect in stroke. Phosphatidylcholine synthesis appears to be impaired after brain ischemia and citicoline can increase levels of phosphatidylcholine by enhancing the rate-limiting enzyme in

its synthesis.[19] *In vitro* evidence also suggests citicoline provides neuroprotection after ischemia by decreasing brain levels of glutamate and increasing ATP levels.[20]

Ischemic Stroke

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.[21] The treatment group (n=133) received 1,000 mg intravenous (I.V.) citicoline daily for 14 days. Compared to 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.

Other trials administering citicoline to post-stroke patients demonstrate 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."[22]

A multicenter, double-blind controlled trial conducted by the Citicoline Stroke Study Group examined the effects of oral citicoline on 259 stroke patients.[23] Three doses of citicoline (500 mg, 1,000 mg, or 2,000 mg) were administered (n=65 in each of three groups) 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, while baseline NIH Stroke Scale (NIHSS) score was assessed as a secondary 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 two times the prospect of stroke recovery compared to patients on placebo; the 2,000-mg group experienced a higher rate of side effects in the form of dizziness and accidental injury. Interestingly, no differences were seen between the 1,000-mg citicoline group and the placebo group.

The Citicoline Stroke Study Group subsequently conducted a second double-blind study similar to the above trial.[24] 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."

Another double-blind, multicenter trial of citicoline included 899 patients with acute ischemic stroke of the middle cerebral artery. The subjects received either 1,000 mg citicoline twice daily or placebo for six weeks, with a six-week, post-treatment follow-up. The primary study end-point – the proportion of patients showing a seven-point or greater improvement from baseline in the NIHSS score – was virtually the same for both groups: 52 percent of patients in the citicoline group and 51 percent in the placebo group. 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.[25]

Hemorrhagic Stroke

Safety and efficacy of citicoline were tested in a double-blind, placebo-controlled trial of 38 patients with hemorrhagic stroke – which usually carries a worse prognosis than ischemic stroke.[26] 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 (CI)=0.55-52.4).

Cognitive Deficits

Memory Impairment/Vascular Dementia

Animal studies in aging rats[27,28] and young dogs[29] demonstrate citicoline can enhance memory and learning.

Memory impairment in the elderly can be due to decreased neurotransmitter formation, poor circulation (vascular dementia), or diseases such as Alzheimer's disease. Citicoline's effectiveness appears to depend on the cause of the impairment.

Citicoline's potential as a treatment for memory impairment associated with aging was studied in a double-blind trial of 84 elderly patients with mild-to-moderate memory loss.[30] The subjects, who 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 results showed acquisition efficiency (AE) improved, while encoding and organization (E-O) and cognitive efficiency (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 of 95 healthy volunteers ages 50-85.[31] During 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 in delayed recall and logical memory as a result of citicoline occurred only in the poor-memory subgroup. At the end of the second phase, greater improvements occurred in the citicoline group, suggesting that 2,000 mg is a more effective daily dose for age-associated memory impairment.

In another double-blind, crossover trial, citicoline was administered orally to 24 memory-impaired elderly subjects for four weeks. Citicoline was given alone at 500-mg 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). Positive effects on recall occurred in all three treatment groups.[32]

A recent meta-analysis reviewed 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.[33]

A small, double-blind clinical trial found no effect of 500 mg citicoline twice daily compared to placebo in 30 patients (n=15 in each group) age 55 or older with moderate-to-severe vascular dementia. Outcomes, assessed after six and 12 months, found no differences between groups in neuropsychological performance at baseline compared to the study end. MRIs showed exacerbation of brain pathology in both groups as the study progressed.[34]

Alzheimer's Disease

Citicoline has demonstrated a possible capacity to improve cognitive performance in early-onset AD (EOAD). In a double-blind, one-month study, 20 AD patients were given 1,000 mg oral citicoline or placebo daily. 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.[35]

A double-blind, placebo-controlled, 12-week trial tested the effect of 1,000 mg citicoline on 30 patients with mild-to-moderate AD. 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 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.[36]

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, late-onset AD (LOAD) patients, and patients with multi-infarct dementia; a fourth group served as control. Increased levels of interleukin-1ß were normalized after three months on citicoline.[37]

Central Nervous System (CNS) Injury

Brain Trauma

Citicoline facilitates memory rehabilitation in brain trauma patients by restoring blood flow to the lesion site.[38] 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.[39]

In a small double-blind study, one month on 1,000 mg oral citicoline daily compared to placebo significantly improved design recall in patients with concussion. No significant differences were observed between the two groups in other tests of cognitive function. In the placebo group, a greater trend toward complaints of post-concussion symptoms such as headache, dizziness, and tinnitus was observed at follow-up.

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.[41] 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.[42]

Neurological Conditions

Parkinson's Disease

Because 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.[43]

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 ATP[20] – it was tested in an experimental model of HD. Citicoline failed to provide protection from neurotoxins used in this study to simulate HD.[44]

Bipolar Disorder and Associated Substance Abuse

Bipolar disorder is associated with high rates of substance abuse, cocaine in particular. In a placebo-controlled trial, 44 subjects with bipolar or schizoaffective disorder were randomized to receive increasing doses of citicoline (week 1=500 mg/day; week 2=1,000 mg/day; week 4=1,500 mg/day; week 6=2,000 mg/day) or placebo for 12 weeks. Because this was an add-on study, participants continued on antipsychotic medications. The citicoline group experienced significant improvements in some measurements of memory and a significant decrease in cocaine use compared to the placebo group; those taking placebo had 6.41-times greater likelihood of a positive urinary test for cocaine. No significant differences were observed in mania or depression between the two groups.[45]

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.[46] 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).[47]

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 that eight years. Citicoline significantly improved visual-evoked potentials and electroretinograms in the citicoline group compared to placebo and baseline.[48]

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.[49]

It is postulated that dopaminergic stimulation is a major mechanism for citicoline's effect on the retina.[50] This hypothesis is bolstered by a recent animal study showing citicoline raises the retinal dopamine concentration in rabbits.[51] Citicoline has demonstrated retinal ganglionic cell regeneration in tissue culture.[52]

Citicoline (1,000 mg I.M. daily) was found to significantly improve visual acuity in patients with amblyopia.[53,54]

Side Effects/Toxicity

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.[55]

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.[56]

The LD_{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_{50} could not be determined as no deaths occurred at the maximum possible oral dose.[57]

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.[58]

The effect of chronic oral consumption of citicoline was studied in dogs 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.[59]

Dosage

Clinical studies indicate the most effective oral dosages for citicoline range from 500-2,000 mg daily. I.V. and I.M. administrations have also used similar dosages.

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