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CDP-Choline

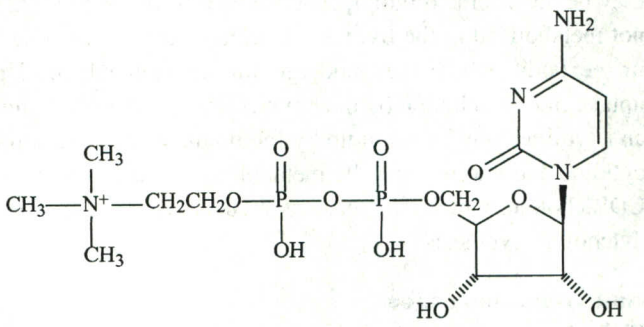
DESCRIPTION

CDP-choline is a naturally occurring substance found in most life forms. It is an intermediate metabolite in the major pathway for the synthesis of phosphatidylcholine. Phosphatidylcholine is a phospholipid that is a major component of cell membranes. Phosphatidylcholine is necessary for the structure and function of all cells and is crucial for sustaining life.

CDP-choline is synthesized in cells by the reaction of the nucleotide cytidine triphosphate or CTP with phosphocholine. The enzyme catalyzing the reaction is called CTP: phosphocholine cytidyltransferase. This reaction is the rate-limiting step in the synthesis of phosphatidyl choline.

Phosphocholine is synthesized from choline, and, for the synthesis of phosphatidylcholine, CDP-choline reacts with diacylglyceride, catalyzed by the enzyme CDP-choline: 1,2-diacylglycerol cholinephosphotransferase.

CDP-choline is also known as cytidine-5′-diphosphate choline and citicoline, and has the following structural formula:



CDP-Choline

ACTIONS AND PHARMACOLOGY

ACTIONS

CDP-choline has putative activity as a cognition enhancer and in cell-membrane repair.

MECHANISM OF ACTION

Since the action of CDP-choline either as a pharmaceutical or nutraceutical agent has yet to be clarified, discussion of its mechanism of action is speculative. However, much is known about the biochemistry of endogenous CDP-choline. CDP-choline is an intermediate metabolite in the major

pathway for the synthesis of the membrane phospholipid, phosphatidylcholine. Phosphatidylcholine is crucial for the maintenance of cell-membrane fluidity and cellular integrity. CDP-choline, hypothetically, may aid in cell-membrane repair, particularly neuronal cell membranes that have been damaged by trauma, ischemic events, toxins, infections or during the course of aging.

CDP-choline is also a delivery form of choline and cytidine. Choline is a precursor of acetylcholine and betaine. Acetylcholine is a neurotransmitter whose deficiency in certain regions of the brain is believed to be an etiological factor in certain dementia syndromes, including Alzheimer's disease. Betaine is involved in the conversion of the amino acid homocysteine to the essential amino acid L-methionine. L-methionine is a protein amino acid. Cytidine, following conversion to cytidine triphosphate, participates in a few reactions, including the formation of CDP-choline and nucleic acids.

PHARMACOKINETICS

Most pharmacokinetic studies have been performed in animals. Following oral intake, most CDP-choline is hydrolyzed in the small intestine to choline and cytidine. Choline and cytidine are absorbed and transported to the liver via the portal circulation. In the liver, choline may enter various metabolic pathways, resulting in the biosynthesis of various substances, including CDP-choline, betaine and phosphatidylcholine. Cytidine enters the cytidine nucleotide pool and may be incorporated into nucleic acids. Choline and cytidine not metabolized in the liver are distributed to various tissues in the body, where they undergo further metabolism. The uptake of CDP-choline by the brain is low. However, choline and cytidine may be taken up by the brain. Within the brain, cytidine and choline may be metabolized via a few steps to CDP-choline, which can serve as a substrate for phosphatidylcholine synthesis.

INDICATIONS AND USAGE

CDP-choline may be useful in the treatment of stroke and brain injury. There is some preliminary evidence that CDP-choline may be helpful in some with tardive dyskinesia, Parkinson's disease, Alzheimer's disease and other conditions characterized by impaired cognitive function, including memory loss. An indication may emerge for it to help improve visual acuity in those with amblyopia.

RESEARCH SUMMARY

In numerous studies of CDP-choline, favorable results have been obtained in cerebral ischemia and traumatic head injury. Its efficacy in these studies has been attributed to its apparent ability to increase phosphatidylcholine synthesis in the brain. In animal studies, it has been shown to enhance cell-membrane formation and repair, to restore intracellular enzyme function, to limit nerve damage and decrease edema.

The same mechanisms, generally, are said to account for favorable effects reported for it in the treatment of Parkinson's disease, Alzheimer's disease and a variety of cognitive disorders, including impaired memory associated with aging.

In a randomized, double-blind, placebo-controlled study, 259 patients with ischemic stroke received placebo or 500 to 2000 milligrams of CDP-choline daily for six weeks commencing within 24 hours of stroke. Among subjects who received 500 milligrams of CDP-choline daily, 53 percent achieved full or nearly-full recovery as measured by tests of neurolgic function. Among those receiving placebo, 33 percent achieved similar levels of recovery in the same time frame. The 500 milligram dose was as efficacious as higher doses and produced no significant side effects. Higher doses produced dizziness in some. Research continues.

One study showed that oral CDP-choline, administered within the first 24 hours after onset in patients with moderate to severe ischemic stroke, significantly increased the probability of complete recovery at three months. A recent rat study evidenced a synergistic effect on infarct size and neuronal death by CDP-choline and reperfusion induced by thrombolysis. (Thrombolysis is still the only generally accepted therapy in acute ischemic stroke.) This combined therapy was superior to either alone in reducing ischemic brain damage. A meta-analysis identified CDP-choline as the first clinically effective neuroprotective agent in ischemic stroke. The placebo-controlled, randomized, double-blind prospective trials evaluated in the meta-analysis used daily oral doses of CDP-choline in the 500-2,000 milligram range for six weeks and involved 1,500 patients in all. While functional recovery was significantly better than in placebo groups, there was less evidence of diminished neurological deficit. Larger trials are underway.

In one study, CDP-choline, given in a daily dose of 1000 milligrams for a month, slightly improved mental performance in subjects with Alzheimer's disease. Better results have been reported with similar doses of CDP-choline in patients with early-onset Alzheimer's disease. Both favorable immunogenic and neurotrophic effects are reported in many of these CDP-choline/Alzheimer's studies.

In a randomized, double-blind, placebo-controlled study, subjects, aged 50 to 85, received placebo or varying doses of CDP-choline, generally 1000 to 2000 milligrams a day, for several months. A subgroup of these subjects, shown to have relatively inefficient memories, benefited the most from CDP-choline, as measured by tests of logical memory. The researchers concluded: "Citicoline may prove effective in

treating age-related cognitive decline that may be the precursor of dementia."

A review paper found evidence in current research that CDP-choline might improve cognitive function in elderly patients with memory deficits, mild cognitive impairment, and senile dementia of the Alzheimer's type. One recent study reported that dietary CDP-choline supplementation prevents memory impairment caused by impoverished environmental conditions in rats. And in a recent study using a rat model of birth asphyxia, CDP-choline attenuated brain damage.

There is preliminary evidence that CDP-choline might be useful in some disorders of vision. Statistically significant vision improvement was noted in a study of 50 patients with amblyopia treated with CDP-choline for 15 days. The improvement was sustained at a four-month follow-up. More research is warranted.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to a CDP-choline-containing product.

PRECAUTIONS

Because of lack of long-term safety studies, CDP-choline should be avoided by children, pregnant women and nursing mothers. Those who wish to try CDP-choline for a health condition should first discuss its use with his or her physician.

ADVERSE REACTIONS

Adverse reactions reported include epigastric distress, nausea, rash, headache and dizziness.

DOSAGE AND ADMINISTRATION

Citicoline (CDP-choline) is approved in some countries as a parenteral drug for the treatment of acute ischemic stroke. There are a number of ongoing clinical trials in the United States and other countries studying citicoline for acute stroke (ICTUS Study: International Citicoline Trial on acUte Stroke), for its effects on brain function and behavior in marijuana-dependent individuals, and as add-on therapy for patients with bipolar disorder and major depression. (See: ClinicalTrials.gov.)

CDP-choline is also being marketed by itself and along with other ingredients as a nutritional supplement, typically 250 milligrams, once or twice daily. Choline makes up approximately 21% of CDP-choline.

Stability is a concern with CDP-choline. Long-alkyl chain sulfonate salts of CDP-choline appear to show enhanced stability for oral use.

LITERATURE

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Cetyl Myristoleate

DESCRIPTION

Cetyl myristoleate is an ester comprised of the 16-carbon atom alcohol, 1-hexadecanol (cetyl alcohol), and the 14-