

## CDP Choline Overview

Cytidine diphosphate choline is the active form of choline normally produced within the body. CDP choline is important for the synthesis of phosphatidylcholine in cell membranes. Choline is a substance required by the brain to produce acetylcholine, a major brain/motor neuron neurotransmitter that facilitates the transmission of impulses between neurons. CDP-choline stands for cytidine-5-diphosphocholine. This unique form of choline readily passes through the blood-brain barrier (BBB) directly into the brain tissue. Once past the BBB, CDP-choline activates the synthesis of critical components in cell membranes and may enhance cerebral energy metabolism.

See Choline Overview

(Source: <http://www.health-marketplace.com/CDP-Choline.htm>)

## Research Overview

The following studies showed that CDP Choline:

1. Affects brain phospholipids concentration
2. Improves verbal memory in aging.
3. May reverse age related changes in the brain.
4. May prevent age related cognitive decline that may be the precursor of dementia.
5. Is a valid therapeutic remedy for the clinical, functional and social recovery of geriatric patients.
6. Influences cognitive and cerebrovascular function in Alzheimer's
7. disease.
8. Diminished histamine (in Alzheimer's disease) and interleukin1 levels in blood and serum, respectively, and increased plasma TNF.
9. Decreased brain damage following traumatic brain injury.
10. Exerts a neuroprotective effect by inhibiting the apoptotic pathway induced by glutamate.
11. Provides choline for synthesis of neurotransmitter acetylcholine, stimulation of tyrosine hydroxylase activity and dopamine release.
12. Treatment within the first 24 hours after onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months.
13. Reduction in ischemic lesion volume growth from baseline to week 12 and a significantly greater reduction in volume from week 1 to week 12.
14. Appears to improve functional outcome and reduce neurologic deficit with 500 mg appearing to be the optimal dose.
15. Provides significant neuroprotection during cerebral ischemia that significantly reduces mortality.
16. In a doubleblind, placebocontrolled study, treatment of glaucoma resulted in functional improvement in the visual system noted with electrophysiological methods
17. Further research is being done on Parkinson's disease and epilepsy.

CDP Choline Abstracts (26)

1\_ J Nutr Biochem. 1992 Jun;3(6):3135.

Effects of orally administered cytidine 5'diphosphate choline on brain phospholipid content.

Lopez GCoviella I, Agut J, Ortiz JA, Wurtman RJ.

Cytidine, as cytidine 5'diphosphate choline (CDPcholine), is important for the synthesis of phosphatidylcholine in cell membranes. To investigate whether exogenous CDPcholine could affect brain phospholipid composition, we supplemented the diet of mice with this drug (500 mg/kg/day) for 27 months in 3monthold mice and for 90, 42, and 3 days in 12monthold mice, and measured their levels of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and the content of phosphatidylinositol plus phosphatidic acid in the cerebral cortex. After 27 months of treatment, PC and PE increased significantly by 19% ( $P < 0.05$ ) and by 20% ( $P < 0.01$ ), respectively. PS levels increased by 18% (not statistically significant). Similar elevations in PC and PE levels were obtained when older mice were treated for only 3 months ( $P < 0.05$ ). No changes were observed with shorter treatment periods. These results suggest that chronic administration of CDPcholine can have effects on brain phospholipid composition that may underlie its reported utility in various neurologic disorders.

2\_ Arch Neurol. 1996 May;53(5):4418.

Citicoline improves verbal memory in aging.

Spiers PA, Myers D, Hochanadel GS, Lieberman HR, Wurtman RJ.

**OBJECTIVE:** To test the verbal memory of older volunteers given citicoline. **DESIGN:** A randomized, double blind, placebo controlled, parallel group design was employed in the initial study. After data analysis, a subgroup was identified whose members had relatively inefficient memories. These subjects were recruited for a second study that used a crossover design. The subjects took either placebo or citicoline, 1000 mg/d, for 3 months in the initial study. In the crossover study, subjects took both placebo and citicoline, 2000 mg/d, each for 2 months. **SUBJECTS:** The subjects were 47 female and 48 male volunteers 50 to 85 years old. They were screened for dementia, memory disorders, and other neurological problems. Of the subjects with relatively inefficient memories, 32 participated in the crossover study. **MAIN OUTCOME MEASURE:** Verbal memory was tested at each study visit using a logical memory passage. Plasma choline concentrations were measured at baseline; at days 30, 60, and 90 in the initial study; and at day 60 of each treatment condition in the crossover study. Plasma choline concentrations and memory scores were analyzed using repeated measures analysis of variance and covariance, followed by planned comparisons when appropriate. **RESULTS:** In the initial study, citicoline therapy improved delayed recall on logical memory only for the subjects with relatively inefficient memories. In the crossover study, the higher dosage of citicoline was clearly associated with improved immediate and delayed logical memory. **CONCLUSIONS:** Citicoline therapy improved verbal memory functioning in older individuals with relatively inefficient memories. Citicoline may prove effective in treating age related cognitive decline that may be the precursor of dementia.

3\_ Methods Find Exp Clin Pharmacol. 1997 Apr;19(3):20110.

Citicoline improves memory performance in elderly subjects.

Alvarez XA, Laredo M, Corzo D, FernandezNovoa L, Mouzo R, Perea JE, Daniele D, Cacabelos R.

Citicoline is a choline donor involved in the biosynthesis of brain phospholipids and acetylcholine extensively used in the treatment of neurodegenerative diseases. In this study we investigated the effects of the oral administration of citicoline alone (C1000:1000 mg/day; C500:500 mg/day) or in combination with nimodipine (C +NI:300 + 90 mg/day) during 4 weeks on memory performance in elderly subjects with memory deficits and without dementia ( $N = 24$ ; age =  $66.12 \pm 10.78$  years; MMS score =  $31.69 \pm 2.76$ ). Results indicated that citicoline in comparison with placebo improves memory in free recall tasks, but not in recognition tests. A significant improvement in word recall ( $5.17 \pm 1.1$  vs.  $3.95 \pm 1.2$  omissions;  $p < 0.005$ ), immediate object recall ( $6.5 \pm 1.6$  vs.  $5.5 \pm 1.2$  omission;  $p < 0.05$ ) and delayed object recall ( $8.5 \pm 2.1$  vs.  $6.7 \pm 2.4$  omissions;  $p < 0.005$ ) was observed after citicoline treatment. Similar results were found in the three subgroups of treatment (8 subjects per group), suggesting that citicoline possesses memoryenhancing activity at doses of 3001000 mg/day. A decrease in systolic blood pressure and minor changes in lymphocyte cell counting were also observed in old subjects after receiving citicoline. These effects are consistent with the vasoregulatory and neuroimmune actions of citicoline and suggest that this compound may improve memory by acting on mechanisms of brain neurotropism and cerebrovascular regulation. According to the present results, showing that citicoline improves memory performance in elderly subjects, we concluded that this molecule is suitable for the treatment of memory deficits in old people.

4\_ Psychopharmacology (Berl). 2002 May;161(3):24854. Epub 2002 Mar 22.

Chronic citicoline increases phosphodiesterases in the brains of healthy older subjects: an in vivo phosphorus magnetic resonance spectroscopy study.

Babb SM, Wald LL, Cohen BM, Villafuerte RA, Gruber SA, Yurgelun-Todd DA, Renshaw PF.

**RATIONALE:** Phosphatidylcholine (PtdCho) in brain cell membranes decreases with age. Evidence from both animal and in vitro studies indicates that CDPcholine (citicoline) administration may increase phosphatidylcholine (PtdCho) synthesis and might reverse PtdCho loss. **OBJECTIVES:** We investigated whether oral citicoline can increase PtdCho synthesis in the brains of older subjects by measuring levels of phosphorus-containing metabolites using proton-decoupled phosphorus magnetic resonance spectroscopy ((<sup>31</sup>)PMRS) before and after citicoline treatment. **METHODS:** All subjects took 500 mg citicoline once orally each day for 6 weeks, then took either citicoline or placebo once orally per day for a second 6-week period. Subjects underwent a (<sup>31</sup>)PMRS scan at baseline and following 6 and 12 weeks of treatment. **RESULTS:** Treatment with citicoline for 6 weeks was associated with a 7.3% increase from baseline levels in brain phosphodiesterases (  $P=0.008$ ), including an 11.6% increase in glycerophosphoethanolamine (  $P=0.002$ ) and a 5.1% increase in glycerophosphocholine (  $P=0.137$ ). Subjects who continued to take citicoline for the second 6-week period did not show significant additional increases in the levels of these metabolites. No changes were seen in other phosphorus-containing metabolites. There was a correlation between improvement on the California Verbal Learning Test and increase in phosphodiesterases. **CONCLUSIONS:** The increases in phosphodiesterases seen in this study indicate that phospholipid synthesis and turnover were stimulated by 6 weeks of oral citicoline. These results in humans support previous in vitro and animal studies and suggest that the administration of oral citicoline may be of use in reversing age-related changes in the brain.

5\_ Clin Ter. 1991 Jun 30;137(6):40313.

[Citicoline in the treatment of cognitive and behavioral disorders in pathologic senile decline]

Di Trapani G, Fioravanti M.

A three-month study was performed on 150 aging patients with primary memory deficits in order to verify the effectiveness of CDPcholine, administered in repeated cycles of four weeks, with an interval of one week between cycles, in improving patients' cognitive and behavioral efficiency and in stabilizing their cognitive decline. Objective measures of memory and attention, and a behavioral rating scale were used to assess treatment effects. CDPcholine treatment demonstrated both symptomatic efficacy and a long-lasting effect on cognition and behavior of these patients. Level of activation and attention responsiveness improved during treatment cycles and no further changes were identified of these variables in the follow-up period. Measures related to specific memory functioning showed, besides improvements during treatment, after-effects still active in the follow-up period, suggesting a long-lasting change of the cognitive decline trend characteristic of these patients.

6\_ Prog Neuropsychopharmacol Biol Psychiatry. 2003 Jun;27(4):7117.

Dietary cytidine (5')diphosphocholine supplementation protects against development of memory deficits in aging rats.

Teather LA, Wurtman RJ.

The present study was designed to assess the effect of supplementation with dietary cytidine (5')diphosphocholine (CDPcholine), a source of cytidine and choline, on memory in young and older rats. Although the hippocampal-dependent memory deficits in aged rats are well documented, cognitive functioning in early aging has not been as thoroughly evaluated. Female Sprague-Dawley rats (3 or 15 months of age) consumed either a control diet or a diet supplemented with CDPcholine (approximately 500 mg/kg/day) for 8 weeks, after which they were trained to perform spatial and cued versions of the Morris water maze. Compared with young rats, aged rats exhibited a selective deficit in spatial memory tasks that required rats to retain information for 24 h or longer. CDPcholine supplementation protected against the development of this deficit, but had no memory-enhancing effect in normal young rats. These findings suggest that early-aged rats display a selective impairment in hippocampal-dependent long-term memory, and that dietary CDPcholine supplementation can protect against this deficit.

7\_ Arzneimittelforschung. 1993 Aug;43(8):8228.

Effects of cytidine diphosphate choline on rats with memory deficits.

Petkov VD, Kehayov RA, Mosharraf AH, Petkov VV, Getova D, Lazarova MB, Vaglenova J.

The effects of cytidine diphosphate choline (CDPcholine, CAS 987780) on learning and memory in rats with memory deficits were examined using behavioral methods of active avoidance with punishment reinforcement (shuttlebox), passive avoidance with punishment reinforcement (step-through and step-down), and active avoidance with positive (alimentary) reinforcement

(staircasemaze). In the majority of experiments CDPcholine was applied orally at doses of 1050 or 100 mg/kg daily for 7 days before the training session. The experiments were carried out on young adult (aged 5 months) and old (aged 22 months) rats and on rats with a low capability for retention of learned behavior. Memory deficits were induced by the muscarinic cholinergic antagonist scopolamine (in young and old rats and mice), by the alpha 2 adrenoceptor agonist clonidine, by electroconvulsive shock, and by hypoxia. Memory deficits were also induced in rats offspring of dams that had been exposed to alcohol during pregnancy and lactation. The results suggest that CDPcholine acts as a memory enhancing drug and that its effect is particularly pronounced in animals with memory deficits.

8\_ Minerva Med. 1990 Jun;81(6):46570.

[Effect of CDPcholine on senile mental deterioration. Multicenter experience on 237 cases]

Serra F, Diaspri GP, Gasbarrini A, Giancane S, Rimondi A, Tame MR, Sakellariadis E, Bernardi M, Gasbarrini G.

The efficacy of CDPcholine (1000 mg/die) administered for two 21 day treatment cycles, with a one week washout period between them, was evaluated in out and inpatients suffering from mild to moderate brain aging. The study was performed on 237 fully evaluable patients with the use of the reduced geriatric scale of Plutchik and al., for clinical evaluation of the symptomatology. The clinical data obtained demonstrate that treatment with CDPcholine is able to determine an improvement of symptomatology since the 1st cycle of therapy ( $p < 0.001$ ), and a further improvement in the 2nd cycle ( $p < 0.001$ ). Particularly, the therapeutic effect of the 1st cycle is persistent in the intermediate washout period (suspension of treatment) with a further decrease, of symptomatology regarding some items of Plutchik's scale ( $p < 0.01$ ). Finally, treatment with CDPcholine 1000 mg/day for two 21 day cycles in 237 patients suffering from brain aging determined a statistically significant improvement of the cognitive and behavioural parameters taken into consideration: independence/autonomous life; human relations/social life; interest and attentive capacity; individual behaviour. Therefore citicoline is confirmed as a valid therapeutic remedy for the clinical, functional and social recovery of these patients.

9\_ Naturforsch [C]. 2003 MarApr;58(34):27781.

Effect of CDPcholine on hippocampal acetylcholinesterase and  $\text{Na}^+, \text{K}^+$  ATPase in adult and aged rats.

Plataras C, Angelogianni P, Tsakiris S.

The aim of this study was to investigate the effect of different cytidine 5' diphosphocholine (CDPcholine) concentrations (0.11 mM) on acetylcholinesterase (AChE),  $\text{Na}^+, \text{K}^+$  ATPase and  $\text{Mg}^{2+}$  ATPase activities in homogenates of adult and aged rat hippocampi. Tissues were homogenised, centrifuged at  $1000 \times g$  for 10 min and in the supernatant, AChE activity and  $\text{Na}^+, \text{K}^+$  ATPase and  $\text{Mg}^{2+}$  ATPase activities were determined according to Ellman's method and Bowler's and Tirri's method, respectively. After an 13 h preincubation of the homogenised tissue with CDPcholine, a maximal AChE stimulation of about 25% for both adult and aged rats ( $p < 0.001$ ) and a  $\text{Na}^+, \text{K}^+$  ATPase activation of about 50% for adult rats ( $p < 0.001$ ) and about 60% for aged rats ( $p < 0.001$ ) were observed, while hippocampal  $\text{Mg}^{2+}$  ATPase activity was not influenced in either adult or aged animals. It is suggested that: CDPcholine can restore hippocampal AChE and  $\text{Na}^+, \text{K}^+$  ATPase activities in the aged rat and thus it may play a role in improving memory performance which is impaired by aging and some neuronal disturbances.

10\_ Methods Find Exp Clin Pharmacol. 1994 Apr;16(3):2118.

Effects of CDPcholine on cognition and cerebral hemodynamics in patients with Alzheimer's disease.

Caamano J, Gomez MJ, Franco A, Cacabelos R.

CDPcholine (cytidine 5' diphosphate choline) is an acetylcholine precursor frequently used in cerebrovascular disorders and psychoorganic syndromes. Furthermore, several authors have demonstrated the positive effects of CDPcholine on cognitive disorders and memory deficits. In the present study, the effects of CDPcholine (1000 mg/day, p.o. for 1 month) on cognition, evaluated by the MiniMental State Examination (MMSE) of Folstein et al., and on blood flow velocities, measured by transcranial Doppler ultrasonography (TCD), were investigated in patients with Alzheimer's disease: (AD,  $n = 20$ , age:  $66.75 \pm 6.73$  years, range: 57-78 yr). Cognitive function was measured by means of the MMSE in basal conditions (A) and after 1 month of treatment with CDPcholine (C). TCD measures were taken through the temporal window for right (MCAR) and left (MCAL) middle cerebral arteries with a 2 MHz pulsed transducer using a TC2000S in basal conditions (A), 1 h after the administration of CDPcholine (B) and after 1 month of treatment with CDPcholine (C). MMSE scores were significantly increased ( $p < 0.005$ ) in patients with early onset Alzheimer's disease (EOAD) after CDPcholine treatment. Moreover, the orientation subtest significantly increased in the global group of AD patients ( $p < 0.01$ ) and in EOAD patients ( $p < 0.02$ ). Significant differences ( $p < 0.05$ ) were also found in MCAL and MCAR measures between recordings. These results suggest that CDPcholine influences cognitive and cerebrovascular function in Alzheimer's disease, probably through a mechanism linked to an immunogenic and/or neurotrophic effect at the microvascular niche.

11\_ Methods Find Exp Clin Pharmacol. 1999 Nov;21(9):63344.

Doubleblind placebocontrolled study with citicoline in APOE genotyped Alzheimer's disease patients. Effects on cognitive performance, brain bioelectrical activity and cerebral perfusion.

Alvarez XA, Mouzo R, Pichel V, Perez P, Laredo M, FernandezNovoa L, Corzo L, Zas R, Alcaraz M, Secades JJ, Lozano R, Cacabelos R.

Cytidine 5'diphosphocholine (citicoline) is a an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain acetylcholine. Citicoline has been extensively used for the treatment of neurodegenerative disorders associated with head trauma, stroke, brain aging, cerebrovascular pathology and Alzheimer's disease. In this study we have investigated the efficacy and safety of the treatment with citicoline versus placebo in patients with Alzheimer disease. Thirty patients (age = 73.0 +/- 8.5 years; range = 57-87 years) with mild to moderate senile dementia (GDS: stages 36) of the Alzheimer type were included in a doubleblind, randomized and placebocontrolled clinical trial. After a 2week period of drug washout, patients were treated with i) placebo (n = 17; age = 73 +/- 5 years) or ii) 1,000 mg/day of citicoline (n = 13; age = 76 +/- 9 years) for 12 weeks (84 days). Examinations were done at baseline (T0) and after the 12 weeks of treatment (T12). As compared to placebo, citicoline improved cognitive performance in Alzheimer's disease patients with APOE E4 (ADAS: difference between groups = 3.2 +/- 1.8 scores, p < 0.05; ADAScog: difference between groups = 2.3 +/- 1.5, ns); and this improvement on cognition was more pronounced (ADAS, p < 0.01; ADAScog: difference between groups = 2.8 +/- 1.3, p < 0.06) in patients with mild dementia (GDS < 5). Citicoline also increased cerebral blood flow velocities in comparison with placebo (p < 0.05) when transcranial Doppler recordings from both hemispheres were considered together, as well as diastolic velocity in the left middle cerebral artery (p < 0.05). Patients treated with citicoline showed an increase in the percentage of brain bioelectrical activity of alpha (occipital electrodes) and theta type (left side electrodes), accompanied by a decrease in relative delta activity particularly marked in the left temporal lobe. Significant differences with respect to placebo (p < 0.05) were observed for theta activity in several frontoparietotemporal electrodes of the left hemisphere. Treatment with citicoline tended to reduce serum IL1 beta levels, mainly after 4 weeks of administration, with no modified blood histamine content. In addition, neither adverse side effects nor alterations in biological and hematological parameters were induced by citicoline. The present data indicate that citicoline (1,000 mg/day) is well tolerated and improves cognitive performance, cerebral blood perfusion and the brain bioelectrical activity pattern in AD patients. According to our results, it seems that citicoline might be a useful treatment in Alzheimer's disease, and that the efficacy of this compound is greater in patients with mild mental deterioration and/or bearing the epsilon 4 allele of the APOE.

12\_ Ann N Y Acad Sci. 1996 Jan 17;777:399403.

Therapeutic effects of CDPcholine in Alzheimer's disease. Cognition, brain mapping, cerebrovascular hemodynamics, and immune factors.

Cacabelos R, Caamano J, Gomez MJ, FernandezNovoa L, FrancoMaside A, Alvarez XA.

CDPcholine was given to patients with Alzheimer's disease (AD) at a daily dose of 1000 mg/day p.o. for one month. This compound slightly improved mental performance, tended to reduce theta activity in frontotemporal regions, increasing alpha power in occipital areas, and enhanced cerebrovascular perfusion by increasing blood flow velocity and reducing pulsatility and resistance indexes. In addition, CDPcholine diminished histamine and interleukin1 levels in blood and serum, respectively, and increased plasma TNF.

13\_ Methods Find Exp Clin Pharmacol. 1994 May;16(4):27984.

CDPcholine induced blood histamine changes in Alzheimer's disease.

FernandezNovoa L, Alvarez XA, FrancoMaside A, Caamano J, Cacabelos R.

Histamine (HA) is a known neurotransmitter with a wide spectrum of biological actions at the central and peripheral levels. Recently, it has been found that HA is involved in the regulation of immune cell function, acting as an immunomodulator. A hyperactivation in the histaminergic system has been demonstrated in Alzheimer's disease (AD), including increased levels of HA in brain, serum, and cerebrospinal fluid of AD patients. In addition, changes in phospholipid metabolism and neuroimmune function have been reported in AD. CDPcholine (cytidine5diphosphatecholine) participates in the phospholipid metabolism pathway incorporating free choline into phosphatidylcholine and choline plasmalogens in several tissues, including the central nervous system. In this study we have measured the concentration of HA in blood from patients with earlyonset AD (EOAD) and lateonset AD (LOAD) under treatment with CDPcholine (1000 mg p.o. x30 days). HA was measured by high performance liquid chromatography (HPLC) with fluorometric detection. CDPcholine reduced the basal levels of blood HA in both EOAD and LOAD by 2fold. The reduction in blood HA content was observed 2 h after CDPcholine administration and gradually progressed for 30 days of treatment. These results confirm the potential immunogenic effects of CDPcholine and also that an excess of HA might influence

some etiopathogenic events in AD.

14\_ J Neurosurg. 2003 Apr;98(4):86773.

Cytidinediphosphocholine treatment to decrease traumatic brain injury induced hippocampal neuronal death, cortical contusion volume, and neurological dysfunction in rats.

Dempsey RJ, Raghavendra Rao VL.

OBJECT: In previous studies at their laboratory the authors showed that cytidinediphosphocholine (CDPcholine), an intermediate of phosphatidylcholine synthesis, decreases edema formation and bloodbrain barrier disruption following traumatic brain injury (TBI). In the present study the authors investigate whether CDPcholine protects hippocampal neurons after controlled cortical impact (CCI)induced TBI in adult rats. METHODS: After adult male SpragueDawley rats had been anesthetized with halothane, a moderategrade TBI was induced with the aid of a CCI device set at a velocity of 3 m/second, creating a 2mm deformation. Shamoperated rats, which underwent craniectomy without impact served as controls. The CDPcholine (100, 200, and 400 mg/kg body weight) or saline was injected into the animals twice (once immediately postinjury and once 6 hours postinjury). Seven days after the injury, the rats were neurologically evaluated and killed, and the number of hippocampal neurons was estimated by examining thioninestained brain sections. By 7 days postinjury, there was a significant amount of neuronal death in the ipsilateral hippocampus in the CA2 (by 53 +/- 7%,  $p < 0.05$ ) and CA3 (by 59 +/- 9%,  $p < 0.05$ ) regions and a contusion (volume 34 +/- 8 mm<sup>3</sup>) in the ipsilateral cortex compared with shamoperated control animals. Rats subjected to TBI also displayed severe neurological deficit at 7 days postinjury. Treating rats with CDPcholine (200 and 400 mg/kg, intraperitoneally) significantly prevented TBIinduced neuronal loss in the hippocampus, decreased cortical contusion volume, and improved neurological recovery. CONCLUSIONS: Treatment with CDPcholine decreased brain damage following TBI.

15\_ J Neurol Sci. 1991 Jul;103 Suppl:S158.

Effects of CDPcholine on the recovery of patients with head injury.

Calatayud Maldonado V, Calatayud Perez JB, Aso Escario J.

A single blind randomized study has been conducted in 216 patients with severe or moderate head injury, with the aim of comparing the evolution of those that received only conventional treatment with the evolution of those treated with CDPcholine. Our results indicate that CDPcholine improves the global outcome of patients. We have found a trend towards a greater improvement in motor, cognitive and psychic alterations in the patients treated with CDPcholine, as well as a shortening of the stay in the hospital ward in the patients receiving this drug that initially presented with severe head injuries.

Neuroprotection

16. J Mol Neurosci. 2003 Feb;20(1):5360.

CDPcholine prevents glutamatediated cell death in cerebellar granule neurons.

Mir C, Clotet J, Aledo R, Durany N, Argemi J, Lozano R, CervosNavarro J, Casals N.

Cytidine 5'diphosphocholine (CDPcholine) has been shown to reduce neuronal degeneration induced in central nervous system (CNS) injury. However, the precise mechanism underlying the neuroprotective properties of this molecule is still unknown. Excitotoxicity causes cell death in CNS injury (trauma or ischemia) and has also been involved in neurodegenerative diseases. We have examined whether CDPcholine prevents glutamatediated cell death, determined by trypan blue exclusion and lactate dehydrogenase activity assays. Pretreatment of rat cerebellar granule cells (CGCs) with CDPcholine causes a dose and timedependent reduction of glutamateinduced excitotoxicity. Cell death is prevented >50% when 100 microM CDPcholine is added 6 d before the glutamate excitotoxic insult but less than 20% when added concomitantly with glutamate. Pretreatment of CGCs with CDPcholine reduces almost completely (>80%) the number of apoptotic cells analyzed by flow cytometry, suggesting that CDPcholine exerts a neuroprotective effect by inhibiting the apoptotic pathway induced by glutamate.

17\_ J Neurochem. 2002 Jan;80(1):1223.

Citicoline: neuroprotective mechanisms in cerebral ischemia.

Adibhatla RM, Hatcher JF, Dempsey RJ.

Cytidine5'diphosphocholine (citicoline or CDPcholine), an intermediate in the biosynthesis of phosphatidylcholine (PtdCho), has

shown beneficial effects in a number of CNS injury models and pathological conditions of the brain. Citicoline improved the outcome in several phase III clinical trials of stroke, but provided inconclusive results in recent clinical trials. The therapeutic action of citicoline is thought to be caused by stimulation of PtdCho synthesis in the injured brain, although the experimental evidence for this is limited. This review attempts to shed some light on the properties of citicoline that are responsible for its effectiveness. Our studies in transient cerebral ischemia suggest that citicoline might enhance reconstruction (synthesis) of PtdCho and sphingomyelin, but could act by inhibiting the destructive processes (activation of phospholipases). Citicoline neuroprotection may include: (i) preserving cardiolipin (an exclusive inner mitochondrial membrane component) and sphingomyelin; (ii) preserving the arachidonic acid content of PtdCho and phosphatidylethanolamine; (iii) partially restoring PtdCho levels; (iv) stimulating glutathione synthesis and glutathione reductase activity; (v) attenuating lipid peroxidation; and (vi) restoring Na<sup>(+)</sup>/K<sup>(+)</sup>ATPase activity. These observed effects of citicoline could be explained by the attenuation of phospholipase A<sub>2</sub> activation. Based on these findings, a singular unifying mechanism has been hypothesized. Citicoline also provides choline for synthesis of neurotransmitter acetylcholine, stimulation of tyrosine hydroxylase activity and dopamine release.

18\_ J Neurosci Res. 1999 Dec 1;58(5):697705.

CDPcholine: neuroprotection in transient forebrain ischemia of gerbils.

Rao AM, Hatcher JF, Dempsey RJ.

CDPcholine is a rate-limiting intermediate in the biosynthesis of phosphatidylcholine (PtdCho), an important component of the neural cell membrane. The ability of CDPcholine to alter phospholipid metabolism is an important function in the treatment of ischemic injury. Exogenous treatment with CDPcholine stimulates PtdCho synthesis and prevents release of free fatty acids (FFA), especially arachidonic acid (AA), after ischemia/reperfusion. Phase III clinical trials of CDPcholine in the treatment of stroke are currently underway. Here we report the neuroprotection by CDPcholine in transient forebrain ischemia of gerbils. CDPcholine significantly attenuated the blood-brain barrier (BBB) dysfunction after ischemia with 6hr reperfusion, and considerably reduced the increase of AA in FFA and leukotriene C<sub>4</sub> (LTC<sub>4</sub>) synthesis at 1 day. Edema was significantly elevated after 1 and 2 days, but attained maximum at 3 day reperfusion. CDPcholine substantially attenuated edema at 3 days. Ischemia resulted in 80 ± 8% CA<sub>1</sub> hippocampal neuronal death after 6 day reperfusion, and CDPcholine provided 65 ± 6% neuroprotection. CDPcholine may act by increasing PtdCho synthesis via two pathways: (1) conversion of 1, 2-diacylglycerol to PtdCho, and (2) biosynthesis of Sadenosylmethionine, thus stabilizing the membrane and reducing AA release and metabolism to leukotriene C<sub>4</sub>. This would result in decreased toxicity due to AA, leukotrienes, oxygen radicals, lipid peroxidation, and altered glutamate uptake, thus limiting BBB dysfunction, edema and providing neuroprotection. Copyright 1999 Wiley-Liss, Inc.

19\_ Folia Neuropathol. 2001;39(3):1415.

CDPcholine, but not cytidine, protects hippocampal CA<sub>1</sub> neurones in the gerbil following transient forebrain ischaemia.

Grieb P, Gadamski R, Wojda R, Janisz M.

The effects of CDPcholine (citicoline), cytidine monophosphate or cytidine on the number of CA<sub>1</sub> hippocampal neurones surviving five minute forebrain ischaemia have been evaluated in gerbils. The substances tested were given in daily doses equivalent on a molar basis to 500 mg/kg CDPcholine, starting immediately after ischaemia. On day five the brains were perfused, postfixed, cut into 10 microm slices and stained with cresyl violet, and the number of neurones in the CA<sub>1</sub> sectors was counted manually under a light microscope at magnification x 400. The results indicate a significant degree of protection provided by citicoline, but no protection by cytidine monophosphate or cytidine. The choline moiety of CDPcholine appears to be essential for the neuroprotective properties of the drug.

20\_ Stroke. 2002 Dec;33(12):28507.

Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials.

Davalos A, Castillo J, Alvarez-Sabin J, Secades JJ, Mercadal J, Lopez S, Cobo E, Warach S, Sherman D, Clark WM, Lozano R.

**BACKGROUND AND PURPOSE:** No single neuroprotective agent has been shown to influence outcome after acute stroke. Citicoline has been studied worldwide in many clinical trials with positive findings, but only 1 trial has obtained significant results in the primary efficacy variables. Our objective was to evaluate the effects of oral citicoline in patients with acute ischemic stroke by a data pooling analysis of clinical trials. The primary efficacy end point chosen was the common evaluation of recovery, combining National Institutes of Health Stroke Scale  $\leq 1$ , modified Rankin Scale score  $\leq 1$ , and Barthel Index  $\geq 95$  at 3 months using the generalized estimating equations analysis. **METHODS:** A systematic search of all prospective, randomized, placebo-controlled, double-blind clinical trials with oral citicoline (MEDLINE, Cochrane, and Ferrer Group bibliographic databases) was undertaken. Individual patient data were extracted from each study and pooled in a single data file. The main inclusion criteria included compatible neuroimaging with ischemic stroke, National Institutes of Health Stroke Scale  $\geq 8$ , and prior modified Rankin Scale

score  $\leq 1$ . Four clinical trials using various doses of oral citicoline (500, 1000, and 2000 mg) were identified. RESULTS: Of 1652 randomized patients, 1372 fulfilled the inclusion criteria (583 received placebo, 789 received citicoline). Recovery at 3 months was 25.2% in citicolinetreated patients and 20.2% in placebotreated patients (odds ratio [OR], 1.33; 95% CI, 1.10 to 1.62;  $P=0.0034$ ). The dose showing the largest difference with placebo was 2000 mg, with 27.9% of patients achieving recovery (OR, 1.38; 95% CI, 1.10 to 1.72;  $P=0.0043$ ). The overall safety of citicoline was similar to placebo. CONCLUSIONS: Treatment with oral citicoline within the first 24 hours after onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months.

21. Rev Neurol. 2001 May 115;32(9):81821.

[Neuroprotection in acute ischemic stroke. Practicability of guidelines for treatment]

[Article in Spanish] Fridman EA, Ottaviano F, Fiol M, Javelier A, Perea JE, Ameriso SF.

INTRODUCTION. Fibrinolytic agents are effective in the treatment of acute ischemic stroke. However, logistic and clinical factors limit their use. Neuroprotective drugs pose less risks and can be used even before performance of computed tomography of the brain as they are not detrimental in hemorrhagic stroke. These aspects, in theory, will allow the use of neuroprotective drugs in larger number of patients. OBJECTIVE. To evaluate the feasibility of a neuroprotection protocol and the potential usefulness of citicoline in acute ischemic stroke. PATIENTS AND METHODS. Thirty seven patients admitted with a clinical diagnosis of acute ischemic stroke (later confirmed with computed tomography) received, within 12 hours of onset of symptoms, citicoline 500 mg intravenously in a single bolus daily for 7 days. Neurological outcome in this group was compared with a group of 37 patients admitted during the 6 month period before the initiation of the trial and not treated with citicoline. Groups were matched by National Institute of Health Stroke Scale (NIHSS) on admission. RESULTS. Patients treated with citicoline (aged 69+/14 years) improved on their NIHSS from admission (5.7+/4.2) to discharge (4.7+/4.5),  $p=0.015$ . The control group (aged 60+/17 years) did not change between admission (5.7+/4.3) and discharge (5.2+/3.5), ns. Patients treated within 6 hours of admission ( $n=12$ ) had more substantial improvement, from 5.4+/2.3 on admission to 3.9+/2.9 at discharge,  $p=0.008$ . There were no differences in vascular risk factor profile between the groups. Citicoline was well tolerated in every subject. CONCLUSIONS. A protocol of acute stroke management using neuroprotective agents presents clear logistic advantages allowing the inclusion of larger number of patients. Citicoline appears as a safe and potentially effective option.

22\_ Ann Neurol. 2000 Nov;48(5):71322.

Effect of citicoline on ischemic lesions as measured by diffusion weighted magnetic resonance imaging. Citicoline 010 Investigators.

Warach S, Pettigrew LC, Dashe JF, Pullicino P, Lefkowitz DM, Sabounjian L, Harnett K, Schwiderski U, Gammans R.

We examined the effect of the neuroprotective and neuroreparative agent citicoline on the growth of cerebral ischemic lesions in a doubleblind placebocontrolled study involving patients with acute ischemic stroke using diffusionweighted magnetic resonance imaging (DWI). Patients with acute ischemic stroke symptom onset 24 hours or less before the start of treatment, National Institutes of Health Stroke Scale (NIHSS) scores of 5 or higher, and lesions of 1 to 120 cc in cerebral gray matter by DWI were enrolled. DWI, T2weighted magnetic resonance imaging (MRI), perfusion weighted MRI, and magnetic resonance angiography were obtained at baseline, week 1, and week 12. Citicoline (500 mg/day) was administered orally for 6 weeks, and patients were followed for 12 weeks. The primary assessment was progression of ischemic lesion volume from baseline to 12 weeks as measured by MRI. A total of 100 patients entered the study. The primary MRI analysis included 40 placebotreated patients and 41 citicolinetreated patients with both baseline and week 12 MRI data and failed to demonstrate a significant difference in lesion volume change from baseline to week 12. From baseline to week 12, ischemic lesion volume [all values mean (SE)] expanded by 180% (107) among placebotreated patients compared with 34% (19) among citicolinetreated patients. In a secondary analysis, lesion volume decreased from week 1 to week 12 by 6.9 cc (2.8) on placebo versus 17.2 cc (2.6) on citicoline. Baseline variables that were predictors of change in lesion size over 12 weeks were the volume of hypoperfusion (strongest association), baseline NIHSS score, lesion volume on DWI, arterial lesion by magnetic resonance angiography, and categorized elapsed time ( $<$  or  $=12$  or  $>12$  hours) from stroke onset to first dose. A marked association between lesion volume reduction and improvement of NIHSS score by seven or more points was observed. Significant correlations between lesion volumes and clinical measures were found, replicating values reported in the literature for smaller case series. We observed a reduction in lesion volume growth from baseline to week 12 with citicoline treatment, with a significantly greater reduction in volume from week 1 to week 12 with citicoline. We found a significant inverse relationship between lesion volume change over 12 weeks as measured by MRI and clinical outcome for ischemic stroke. This relationship supports the role of DWI as a surrogate marker of clinically meaningful lesion progression in stroke clinical trials. The hypothesis that citicoline reduces lesion growth and improves clinical outcome will be tested further.

23\_ Neurology. 1997 Sep;49(3):6718.

A randomized dose response trial of citicoline in acute ischemic stroke patients. Citicoline Stroke Study Group.

Clark WM, Warach SJ, Pettigrew LC, Gammans RE, Sabounjian LA.

Citicoline (CDPcholine) is a key intermediary in the biosynthesis of phosphatidylcholine, an important component of the neural cell membrane. It has been shown to produce beneficial effects in both animal models and non US clinical stroke trials. This study comprised a randomized (3 doses of citicoline to 1 placebo), vehicle controlled, double blind trial at 21 US centers. Treatment was to be started within 24 hours of stroke onset and was continued orally for 6 weeks. Final outcome assessments were at 12 weeks. Two hundred fifty-nine patients were enrolled, with approximately 65 in each of the four groups. Mean time from stroke onset to treatment was 14.5 hours, and there were no significant differences in baseline characteristics between the four groups except for patient weight. A significant difference between the groups, favoring citicoline treatment, was seen in terms of functional outcome as measured by the Barthel Index and Rankin scale, neurologic evaluation as measured by the National Institutes of Health (NIH) stroke scale, and cognitive function as measured by the Mini Mental Status Examination. When the baseline NIH stroke scale was used as a covariate, both the 500mg citicoline group and the 2,000mg citicoline group had a significant improvement in terms of the percent of patients who had a favorable outcome on the Barthel Index at 90 days. There were no drug-related serious adverse events or deaths in this study. This study suggests that oral citicoline can be used safely with minimal side effects in acute stroke treatment. Citicoline appears to improve functional outcome and reduce neurologic deficit with 500 mg of citicoline appearing to be the optimal dose.

24\_ Arch Physiol Biochem. 2001 Apr;109(2):1617.

Ischemic brain injury caused by interrupted versus uninterrupted occlusion in hypotensive rats with subarachnoid hemorrhage: neuroprotective effects of citicoline.

Alkan T, Kahveci N, Goren B, Korfali E, Ozluk K.

This study investigated the neuroprotection provided by cytidine 5'diphosphocholine (citicoline) during interrupted and uninterrupted occlusion of the basilar artery after subarachnoid hemorrhage (SAH) in 121 hypotensive rats. Animals were anesthetized and the basilar artery was exposed through a transclival approach. Baseline local cerebral blood flow (LCBF) values were recorded, and then the basilar artery was punctured, causing SAH. Blood was drawn to induce hypotension [6070 mmHg mean arterial blood pressure (MABP)]. Control rats received intraperitoneal (i.p.) injections of 0.5 ml saline immediately after SAH before hypotension induction and after 60 min of occlusion. Experimental rats received 400mg/kg citicoline i.p. at the same time points. Control group I and treatment group III were subjected to 60 min of interrupted occlusion (5 min of reperfusion after each 10 min of occlusion). Control group II and treatment group IV were subjected to 60 min of uninterrupted occlusion. MABP and LCBF were recorded every 5 minutes. Brain edema was evaluated in seven rats from each group at 24 hours after ischemic injury. At 3 days after occlusion, another set of 28 rats was killed and coronal brain slices were stained to assess infarct volume. The groups' physiological and edema findings were similar. In all groups, LCBF fell immediately after SAH and remained below baseline throughout the experiment. In the citicolinetreated rats, arterial pressure increased significantly after 3040 min of occlusion, and brain slices showed significantly smaller infarct volumes compared to control slices ( $p < 0.05$ ). Mortality was significantly lower in the citicolinetreated animals ( $p < 0.001$ ). The results suggest that citicoline provides significant neuroprotection during cerebral ischemia, and that it significantly reduces mortality. Part of the neuroprotective effect may be mediated by recovery of arterial pressure.

25\_ J Neurosci Res. 2002 Jan 15;67(2):1438.

Pharmacodynamics of citicoline relevant to the treatment of glaucoma.

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Citicoline (exogenous CDPcholine) is a nontoxic and welltolerated drug used in pharmacotherapy of brain insufficiency and some other neurological disorders, such as stroke, brain trauma, and Parkinson's disease. A few reports indicate that citicoline treatment may also be beneficial in glaucoma. Currently glaucoma is considered a neurodegenerative disease in which retinal ganglion cells (RGC) slowly die, likely in the apoptotic mechanism. Endogenous CDPcholine is a natural precursor of cellular synthesis of phospholipids, mainly phosphatidylcholine (PtdCho). Enhancement of PtdCho synthesis may counteract neuronal apoptosis and provide neuroprotection. Citicoline, when administered, undergoes a quick transformation to cytidine and choline, which are believed to enter brain cells separately and provide neuroprotection by enhancing PtdCho synthesis; similar effect may be expected to occur in glaucomatous RGC. Furthermore, citicoline stimulates some brain neurotransmitter systems, including the dopaminergic system, and dopamine is known as a major neurotransmitter in retina and postretinal visual pathways. In a doubleblind, placebocontrolled study, treatment of glaucoma resulted in functional improvement in the visual system noted with electrophysiological methods. Development of citicoline as a treatment for glaucoma is indicated. Copyright 2002 WileyLiss, Inc.

26\_ Ophthalmology. 1999 Jun;106(6):112634.

Parisi V, Manni G, Colacino G, Bucci MG.

**PURPOSE:** To evaluate the effects of cytidine5'diphosphocholine (citicoline) on retinal function and on cortical responses in patients with glaucoma. **DESIGN:** Randomized clinical trial. **PARTICIPANTS:** Forty patients with openangle glaucoma were randomly divided into two age-matched groups: citicoline group ([GC] n = 25) and placebo group ([GP] n = 15). **METHODS:** The GC patients were treated with Neuroton (citicoline, 1000 mg/day intramuscularly) for 60 days; GP patients were treated with placebo (physiologic solution with additives) for 60 days. After 120 days of washout (day 180), the GC patients were divided into two age-matched groups: in 10 patients (GC1 group) the washout was prolonged for a further 120 days; in 15 patients (GC2 group) a second 60-day period of citicoline treatment was followed by a second 120-day period of washout. At day 180, the washout was extended for another 180 days in GP patients. In all subjects, retinal and cortical responses were evaluated by simultaneous recordings of visual evoked potentials (VEPs) and pattern electroretinograms (PERGs) at baseline, after 60 days, and after 180 days. At day 300, VEPs and PERGs were also evaluated in GC1 patients, and at 240 and 360 days in GC2 and GP patients. **MAIN OUTCOME MEASURES:** Visual evoked potential parameters (P100 latency and N75P100 amplitude); PERG parameters (P50 latency and P50N95 amplitude); and intraocular pressure. **RESULTS:** The GP patients displayed similar VEP and PERG parameters in all examinations performed. In GC patients, the treatment with citicoline induced a significant ( $P < 0.01$ ) improvement of VEP and PERG parameters, and their values were significantly different ( $P < 0.01$ ) with respect to those of GP patients ( $P < 0.01$ ). Visual evoked potentials and PERGs, recorded in GC patients after washout, revealed that although there was a worsening trend, the electrophysiologic improvement was still maintained. After a second period of washout, GC1 patients had VEP and PERG parameters similar ( $P > 0.05$ ) to baseline ones and to those of GP patients. In GC2 patients, a second period of citicoline treatment induced a further ( $P < 0.01$ ) improvement of VEP and PERG parameters. **CONCLUSION:** Citicoline may induce an improvement of the retinal and of the visual pathway function in patients with glaucoma.

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