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Citicoline: pharmacological and clinical review, 2010 update

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Summary. This review is based on the previous one published in 2006 –Secades JJ, Lorenzo JL. *Citicoline: pharmacological and clinical review, 2006 update*. Methods Find Exp Clin Pharmacol 2006; 28 (Suppl B): S1-56–, incorporating the new references until now, having all the information available to facilitate the access to the información in one document. This review is focused on the main indications of the drug, as acute stroke and its sequelae, including the cognitive impairment, and traumatic brain injury and its sequelae. There are retrieved the most important experimental and clinical data in both indications.

Key words. Alcoholism. Alzheimer disease. Amblyopia. Apoptosis. CDP-choline. Cerebral edema. Cerebral ischemia. Citicoline. Cognitive disorder. Drug addiction. Glaucoma. Head injury. Memory. Neuronal membrane. Neuroplasticity. Neuroprotection. Neurorepair. Neurotransmission. Parkinson disease. Phosphatidylcholine. Phospholipase. Senile dementia. Stroke. Structural phospholipids. Traumatic brain injury.

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Introduction

Phospholipids are essential constituents of cells, specifically cell membranes, and have a high turnover rate, which necessitates the continuous synthesis of these compounds to ensure the adequate function of cell membranes and, therefore, cells [1-3].

The chemical structure of a phospholipid shows esterification of a polyalcohol (glycerol or sphingosine) with two long-chain fatty acids and a molecule of phosphoric acid that is esterified with nitrogenated bases (choline, ethanolamine), amino acids (serine) or inositol [3,4]. The main phospholipids in humans are phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and sphingomyelin [4]. The main function of phospholipids is to serve as components of cell membrane structures; these compounds are indispensable in fulfilling membrane functions, particularly the maintenance of homeostasis and cell compartmentalisation, enzymatic activities associated with membrane systems and coupling between receptors and intracellular signals [1]. Additional specific functions of neuronal membranes include nerve impulse conduction and neurotransmission [1,5].

There are various conditions in which the loss or decreased synthesis of a phospholipid occurs, leading to impairments in cell functions that may have pathophysiological impacts [1,6]. In the central nervous system, structural phospholipids of the neuronal membrane are essential for adequate brain maturation [7-9], including the maturation of astroglial cells [10]. Impaired cell membranes and phospholipid metabolism have been implicated in the pathophysiology of cerebral oedema and traumatic brain injury (TBI) [11-20], cerebral hypoxia [21,22] and cerebral ischaemia [23-26]. Moreover, there are specific changes in neuronal membranes and the metabolism of structural phospholipids associated with brain ageing [37-39] that contribute to neuroplasticity mechanisms [53] in certain neurodegenerative diseases, such as cognitive impairment, vascular dementia, and senile dementia of the Alzheimer type [32,40-52], and in other conditions where changes in neurotransmission [54,55,57] and excitotoxic aggression [58,59] are involved. Changes in phospholipid metabolism, particularly changes in phosphatidylcholine metabolism, have been implicated as mechanisms that trigger the apoptotic cascade in a number of conditions [56-64]. Because of these pathophysiological conditions, there is a need to develop drugs that accelerate and/or increase the synthesis of membrane structural phospholipids in such situations, which would have protective, restorative and reparative effects on the nervous system [65-70].

Figure 1. Chemical structure of CDP-choline (citicoline).

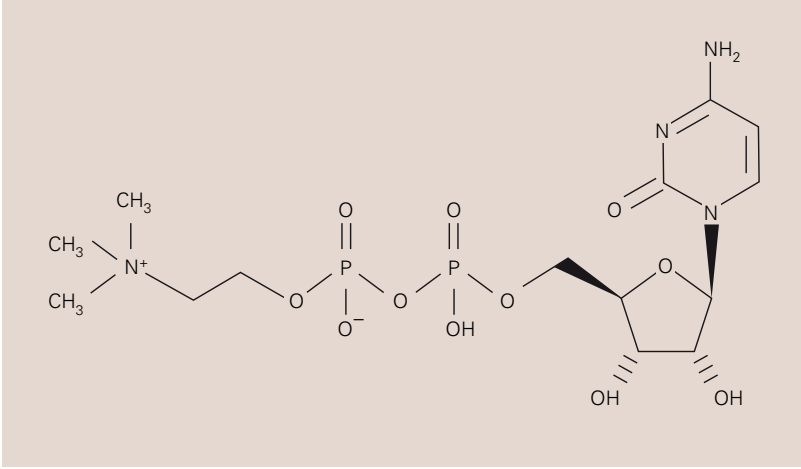
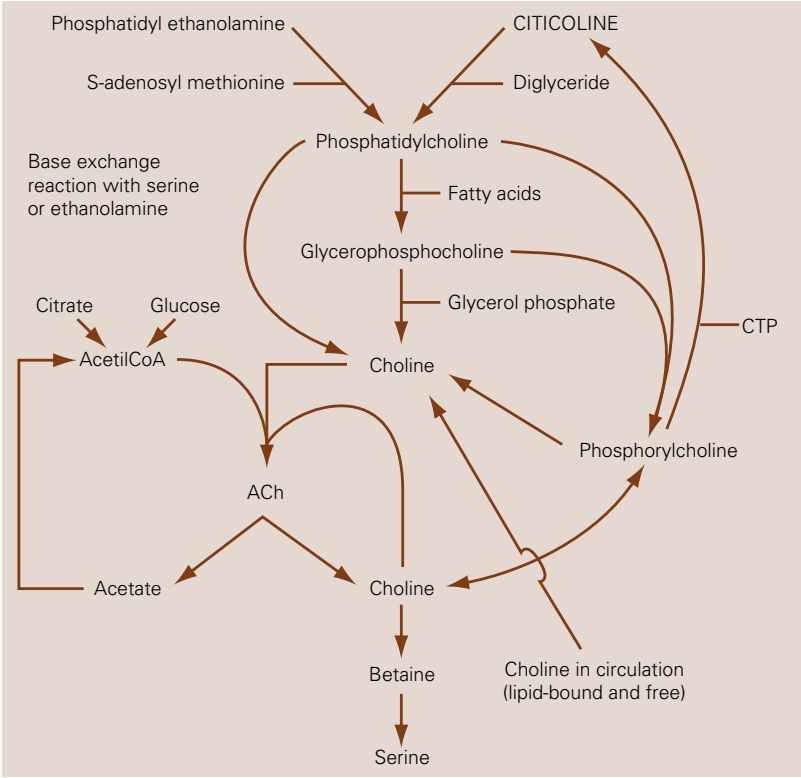


Figure 2. Relationship between citicoline and choline metabolism, cerebral phospholipids and acetylcholine.



Cytidine diphosphocholine (CDP-choline or citicoline) is a mononucleotide consisting of ribose, cytosine, pyrophosphate, and choline whose chemical structure (Figure 1) corresponds to 2-oxy-4-aminopyrimidine [71]. CDP-choline is an essential intermediate in the synthesis of structural phospholipids of cell membranes [4,72-85], and the formation of this compound from phosphorylcholine is the rate-limiting step of this biosynthetic pathway [75,86-95]. As shown in Figure 2, CDP-choline is also related to acetylcholine metabolism. Thus, citicoline administration serves as an exogenous choline source for acetylcholine synthesis, as will be discussed later.

Pharmacological actions

Traumatic lesions and experimental cerebral oedema

Horrocks et al [96] have shown that citicoline and CDP-ethanolamine prevent the degradation of choline and ethanolamine phospholipids during decapitation ischaemia in rats and induce a partial reversion of free fatty acid release during reperfusion after experimental global ischaemia in gerbils. Citicoline and CDP-ethanolamine, when administered together, have a synergistic effect and stimulate the resynthesis of choline, ethanolamine, and inositol phospholipids, markedly decreasing free arachidonic acid levels.

In an experimental rat model of acute induced ischaemia, LePoncin-Lafitte et al [97] assessed the integrity of the blood-brain barrier (BBB) with labeled iodinated albumin and assessed brain metabolism with histoenzymological studies . In this experimental model, citicoline administration resulted in a reduction in vasogenic cerebral oedema and a restoration of BBB integrity. LePoncin-Lafitte et al [97] found that the size of induced infarcts was smaller after citicoline treatment, and this compound decreased the activity of lactate dehydrogenase, succinyl dehydrogenase, monoamine oxidase, and acid phosphatase, emphasising its protective role through direct activity at the level of the cell membrane.

Mykita et al [98] found that the addition of citicoline following a hypocapnic lesion in neuronal cultures resulted in neuron protection. Hypocapnia increases the incorporation of labelled choline into phospholipids, whereas this process is slowed in the presence of citicoline. These authors concluded that citicoline is able to protect neurons un-

der conditions of alkalosis and may promote cell proliferation.

In an electrophysiological study in rabbits, Yasuhara et al [99,100] showed that citicoline decreased the threshold for the arousal reaction and the threshold for muscle discharge, and they concluded that citicoline is a valuable drug for the treatment of brain lesions because of its effects on consciousness and on the motor activity of the pyramidal system and its afferent pathways.

Martí-Viaño et al [101] compared the effects of pyriglutine, piracetam, centrophenoxine, and citicoline in a study on the antagonism of barbiturate coma in mice. No differences were seen in animals treated with pyriglutine, piracetam or centrophenoxine compared to the control group, whereas with citicoline, coma duration and depth, as well as respiratory depression, were decreased compared to all other groups. The arousal effects of citicoline were found to be due to increased cerebral blood flow (CBF), improved O_2 cerebral uptake and utilisation of energy metabolism, and enhanced mitochondrial breathing.

In an experimental model of head injury in monkeys, Ogashiwa et al [102] established a significant dose-effect relationship between citicoline dose and coma duration, which started to be significant at doses of 60 mg/kg ($p < 0.05$). While studying the effects of several activators of brain metabolism, Watanabe et al [103] found that citicoline increased glucose incorporation and metabolism and decreased lactate accumulation in the brain and induced a slight increase in CBF.

In a study on nerve tissue responses to a contusion lesion, Alberghina et al [11] showed that a moderate increase in the activity of cholinephosphotransferase occurred and that the increase was associated with a greater increase in the activity of phospholipases A_2 and several lysosomal hydrolases. They also found an increased number and size of lysosomes during neuronal regeneration. Arrigoni et al [104] showed that citicoline completely inhibits the activation of phospholipase A_2 without altering cholinephosphotransferase activity. However, Freysz et al [105] showed that, in addition to decreasing the activity of phospholipases A_1 and A_2, citicoline decreases free fatty acid release under hypoxic conditions, adding a protective effect to its activating capacity of phospholipid reconstruction. Massarelli et al [106] showed modulation of the activity of the phospholipases A_1, and agreed with Alberghina and Giuffrida [11], Arrigoni et al [104], Freysz et al [105] in their conclusions. Kitazaki et al [107] also showed an inhibitory effect of citicoline on membrane-associated phospholipase A_2 in the rat brain cortex. Based on these characteristics, citicoline is considered to be a non-specific inhibitor of phospholipase A_2 at the intracellular level [108].

Algate et al [109] tested the effects of citicoline in an experimental model of epidural compression in anaesthetised cats. They noted that animals treated with citicoline had a greater resistance to the effects of mechanical brain compression compared to animals in the control group. They also found that respiratory and cardiovascular changes were less intense in treated animals and concluded that citicoline provides significant protection against the lethality of epidural compression. These results agreed with those obtained by Hayaishi [110] and Kondo [111], who showed an improvement in EEG tracing and survival quality following the administration of citicoline to cats undergoing experimental brain compression.

Tsuchida et al [112] administered ^{3}H-citicoline by intraperitoneal injection to rats subjected to cerebral cryogenic lesions by dry ice application on the scalp and confirmed the presence of labelled drug in the brain parenchyma, particularly in the white matter and most commonly in damaged areas of the parenchyma in general.

Boismare [12,113] conducted research on an experimental model of craniocervical trauma without a direct blow ('whiplash') to assess its effects on central catecholamine levels. These experiments resulted in increased dopamine levels and decreased norepinephrine levels in the brain following trauma. This type of lesion causes postural dysregulation of the brain supply (CBF and nutrients) and behavioural and learning disorders that are related to the accelerated degradation of cerebral norepinephrine. In animals treated with citicoline, trauma did not change the levels of these amines. The author stressed the protective role of citicoline due to its stabilising effect on brain catecholamine levels.

Clendenon et al [114] showed that the decrease in Mg^{++}-dependent ATPase activity in mitochondrial and synaptosomal membranes that occurs in traumatic lesions is prevented by citicoline administration.

In a series of studies on a model of cryogenic cerebral oedema in rabbits, Cohadon et al [14,15, 115] showed that treatment with 20 mg/kg/d citicoline slowed the drop in enzymatic activity of mitochondrial ATPase, restored Na^+/K^+ ATPase activity, restored oligomycin-sensitive ATPase activity and accelerated cerebral oedema reabsorption,

which reached normal values on day 4, whereas such levels were not reached until day 10 with spontaneous reabsorption.

These authors stated that the beneficial activity of citicoline in cerebral oedema occurred through two mechanisms: by restoring the insertion of membrane enzymes and enhancing their activity and by acting on oedema by reducing water imbibition of the brain parenchyma.

Lafuente and Cervós-Navarro [116,117] conducted microgravimetric studies on experimental cerebral oedema induced by ultraviolet radiation in cats to assess the effects of citicoline in this situation. The results suggested that citicoline decreased the amount of oedema, enhanced fluid reabsorption and accelerated fluid drainage to the ventricles, i.e., increased cerebral compliance. The authors concluded that CDPamines are helpful in controlling tissue lesions related to increased free fatty acids and to restore cell energy metabolism by restarting the Na^+/K^+ pump.

Majem et al [118] assessed the EEG changes that occur in rats when cryogenic oedema is induced and how such EEG changes were modified by citicoline administration. These authors noted a significant increase in the theta frequency band during the awake state, with decreased delta and slow alpha bands and less interindividual scatter of the overall frequency bands, which resulted in increased electrogenic cerebral stability. They concluded that citicoline protected brain activity from the effects of cryogenic cerebral oedema.

In an experimental model of cryogenic cerebral oedema, Roda [119] measured extravasation of Evans blue through the BBB and fluorescein uptake by astrocytes and neurons and found that citicoline administration significantly reduced both processes compared to control animals, supporting the theory that citicoline has a direct effect on transmembrane transport of sodium, potassium, water and proteins at both the BBB endothelial cell level and the astrocyte and neuron level. Although the exact mechanism of this action is not completely understood, its effect appears to occur at two levels: on the interface separating capillaries from the neuroglia and on cell membranes.

Dixon et al [120] analysed the effects of exogenous administration of citicoline on motor deficits, spatial memory capacity and acetylcholine levels in the dorsal hippocampus and neocortex in a rat model of traumatic brain lesions induced by a controlled lateral impact. Citicoline was administered intraperitoneally at a dose of 100 mg/kg for 18 days from the first day following traumatic lesion induction. Another group of animals was treated with saline solution. Motor assessments were performed using a balance test for which the animals had previously been trained and cognitive assessments were made with a variant of the Morris maze test, which is sensitive to cholinergic function. Microdialysis methods were also used to analyse the effects upon acetylcholine release. In the motor function study, citicoline-treated animals showed a significantly longer balance period the first day after lesion induction compared to animals receiving saline (39.66 ± 3.2 seconds vs. 30.26 ± 2.9 seconds; $p < 0.01$). In addition, animals treated with citicoline had significantly fewer cognitive deficits. In microdialysis studies, after a single intraperitoneal administration of citicoline, a rapid increase in acetylcholine production in both the dorsal hippocampus ($p < 0.014$) and neocortex ($p < 0.036$), which was maintained for up to 3 hours, was seen compared to baseline, whereas no changes were noted in the animals receiving saline. The authors concluded that post-traumatic deficits in spatial memory function are at least partly due to deficiency changes in cholinergic transmission that are attenuated with citicoline administration.

Plataras et al [121] analysed the effects of different citicoline concentrations (0.1-1 mM) on the activities of acetylcholinesterase, Na^+/K^+-ATPase and Mg^{++}-ATPase in total brain homogenates from rats and extracts of non-membrane-bound pure enzymes. Following 1-3 h of preincubation with citicoline, peak stimulations of 20-25% ($p < 0.001$) and 50-55% ($p < 0.001$) were seen for acetylcholinesterase and Na^+/K^+-ATPase, respectively, whereas no significant effect was seen for Mg^{++}-ATPase. The authors concluded that citicoline may stimulate cerebral acetylcholinesterase and Na^+/K^+-ATPase independently from acetylcholine and norepinephrine, which could partly account for the clinical effects of the drug.

Baskaya et al [122] examined the effects of citicoline on cerebral oedema and BBB rupture in a rat model of traumatic brain injury. Animals received citicoline (50, 100 or 400 mg/kg) or saline twice intraperitoneally following traumatic brain lesion induction. Induction of a traumatic lesion caused an increase in the water content percentage and Evans blue extravasation (a marker of BBB rupture) in the damaged cortex and ipsilateral hippocampus. At 50 mg/kg, citicoline was not effective, whereas at 100 mg/kg, a reduction was seen in Evans blue extravasation in both regions, although this dose only decreased cerebral oedema in the damaged

cortex. A citicoline dose of 400 mg/kg significantly reduced cerebral oedema and BBB rupture in both regions. The authors concluded that these results suggest that citicoline is an effective neuroprotective agent on secondary lesions occurring in association with traumatic cerebral injury.

Using an experimental model of controlled lateral impact in rats, Dempsey and Rao [123] showed that intraperitoneal administration of 200-400 mg/kg citicoline following TBI induction prevents neuronal damage in the hippocampus associated with a traumatic lesion, decreases cortical contusion volume and improves neurological recovery.

A synergistic effect has been demonstrated between propofol and citicoline in an experimental model of TBI in rats [124]. Administration of the two drugs together resulted in a greater reduction in lipidic peroxidation.

In a study on the effects of citicoline on traumatic spinal cord lesions, it was shown that intraperitoneal (i.p.) administration of 300 mg/kg citicoline 5 minutes after lesion induction significantly reduced lipid peroxidation and improved motor function in treated animals [125]. Citicoline administration had the same efficacy as methylprednisolone in behavioural and neuroanatomical recovery [126]. The administration of repeated doses of citicoline prevents tissue damage associated with spinal cord shock in the acute phase [127], and the combination of ischaemic postconditioning with citicoline confers protection in a model of ischaemic spinal cord lesion [128] through inhibition of the caspase pathway and an increase in the levels of antiapoptotic proteins.

Beneficial effects of citicoline have also been observed in experimental models of partial optic nerve crush in rats [129], and some data suggest that citicoline promotes nerve regeneration and reduces postoperative scarring after peripheral nerve surgery [130].

Because of its biochemical, pharmacological and pharmacokinetic characteristics, citicoline is a potentially useful drug for the treatment of traumatic cerebral injuries [131].

Cerebral hypoxia and ischaemia

In vitro studies using nerve tissues have shown that hypoxia induces a time-dependent decrease in the synthesis of structural phospholipids (i.e., the longer the hypoxia, the stronger the impact on neuronal phospholipid metabolism) [132]. Moreover, decreased incorporation of marked precursors into phospholipids of neuronal subcellular fractions in animals subjected to experimental hypoxia has been shown [21]. When cerebral ischaemia is induced experimentally, glycerophospholipids in cell membranes are broken down by the actions of different phospholipases, producing free fatty acids and arachidonic acid derivatives. With prolonged ischaemia, induced aggression upon membranes becomes more intense, and membranes lose their functions. Na^+ and Ca^{2+} accumulate inside the cell, triggering the ischaemic cascade and invariably leading to cell death [6,28,32,36,108,133].

Under ischaemic conditions with the attendant neuronal distress, endogenous CDP-choline synthesis is compromised because under such conditions, the cell lacks the high-energy phosphate compounds necessary for this biosynthetic route [32,134].

Because of the importance of restoring neuronal activity following cerebral ischaemia [4] and based on previous experimental data, many studies have investigated the effects of citicoline in various experimental models of cerebral ischaemia and/or hypoxia.

Boismare et al [135] reported that treatment with 20 mg/kg citicoline i.p. in acutely hypoxic rats induced a decrease in vegetative responses, protection from conditioned avoidance responses and stabilisation of brain dopamine and norepinephrine levels. This same group [136] found increases in blood pressure, heart rate, cardiac output and regional blood flows in dogs subjected to normobaric hypoxia, whereas no changes were observed in total peripheral resistance. Administration of citicoline abolished the haemodynamic effects induced by acute hypoxia, suggesting that this action was correlated with a dopaminergic agonistic effect of the drug. In cats subjected to short periods of cerebral ischaemia, researchers [137] noted that a depression occurred in cortical evoked potentials. This depression was attenuated by prior intracarotid administration of citicoline. These authors believed that the protective effects of citicoline are metabolic/biochemical rather than haemodynamic in origin and do not rule out a direct action of the drug on central dopaminergic structures.

Alberghina et al [138] investigated the effects of citicoline on the incorporation of labelled precursors into cerebral phospholipids of guinea pigs subjected to hypoxia. A group of animals were given 100 mg/kg citicoline i.p. Ten minutes later, the labelled precursors [2-^{3}H]glycerol and [1-^{14}C]palmitate were administered intraventricularly. Another group of animals received precursors only and act-

ed as the control group. Compared to the control group, the citicoline-treated animals showed an increase in specific radioactivity of total lipids and phospholipids in purified mitochondria obtained from the brain hemispheres, cerebellums and brain stems. In a subsequent study, this same group [139] showed that citicoline was able to counteract the effects of hypoxia upon incorporation of labelled precursors into RNA and proteins, particularly at the nuclear and mitochondrial levels.

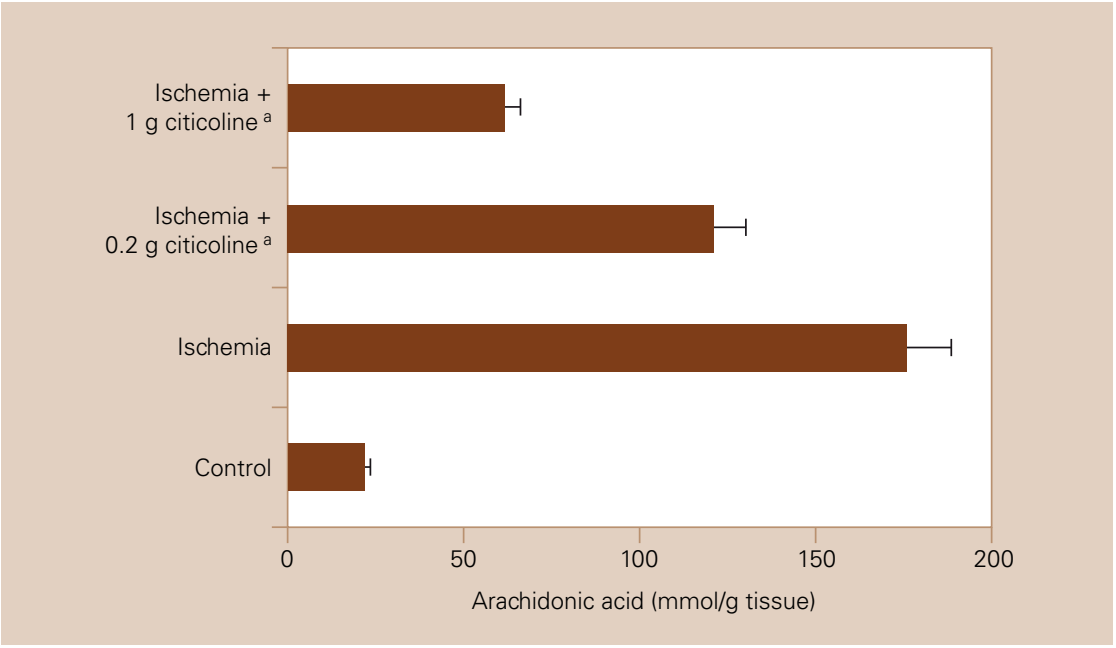
Various experimental studies have shown that citicoline prevents fatty acid release during cerebral ischaemia and hypoxia and increases the synthesis of structural phospholipids [140-159]. Using an experimental model of global cerebral ischaemia by decapitation, Horrocks et al [140,143,145] showed that the administration of a mixture of citicoline and CDP-ethanolamine decreased free fatty acid release and increased synthesis of the corresponding glycerophospholipids, suggesting an involvement of choline and ethanolamine phosphotransferases.

Using an experimental global ischaemia model consisting of bilateral carotid ligation in gerbils, Trovarelli et al [141,142] found that intraperitoneal citicoline administration partially prevents the changes in lipid metabolism that are induced by cerebral ischaemia by correcting the increase in free fatty acid levels, the changes in the levels of neutral lipids such as diacylglycerol and the decrease in phosphatidylcholine levels. Suno and Nagaoka [144] studied the effects of citicoline administration in rats on free fatty acid release caused by total cerebral ischaemia lasting 5 minutes. The tested drug reduced the increase in free fatty acid levels and that the intensity of this effect depended on the dose used. The arachidonic acid levels in brains from control group animals subjected to ischaemia were 174 ± 22 mmol/g, compared to 119 ± 8 mmol/g and 61 ± 8 mmol/g in animals receiving 200 and 1,000 mg/kg i.p. of citicoline, respectively. The authors concluded that citicoline administration prevents ischaemic cerebral damage. Agut et al [146] treated male rats weighing 190-200 g with 4 mg/kg of ^{14}C-methyl-Citicoline (50 μmCi) orally. At 24 hours, brain radioactivity levels and the presence of labelled phospholipids were assessed under conditions of normoxia, hypoxia and hypoxia following an additional administration of 100 mg/kg of unlabeled citicoline. They found marked incorporation of radioactivity into the brains of normoxic and hypoxic animals that was mostly associated with phosphatidylcholine. In addition, the administration of unlabeled citicoline reduced the elevation in cerebral lysophosphatidylcholine levels caused by hypoxia. Rao et al [150] showed that citicoline significantly decreased BBB dysfunction after ischaemia with a 6-hour reperfusion in gerbils and, in the same model of transient cerebral ischaemia, considerably reduced the increase in arachidonic acid and leukotriene C_4 synthesis 24 hours after ischaemia induction. They also showed that the cerebral oedema volume was substantially lower at 3 days in animals treated with citicoline. Following 6 days of reperfusion, ischaemia caused 80 ± 8% neuronal death in the hippocampal CA_1 layer level, and citicoline provided neuroprotection of 65 ± 6%. In a subsequent study, these authors [151] showed that citicoline is able to significantly restore phosphatidylcholine, sphingomyelin and cardiolipin levels after the induction of transient cerebral ischaemia in gerbils. For these authors, the main action mechanism of citicoline would be the inhibition of stimulation of phospholipase A_2 activity in ischaemic conditions, though they also stress its effects on glutathione synthesis and glutathione reductase activity. Thus, the drug may prevent membrane destruction, decrease free radical generation and preserve the natural defences of the nervous system against oxidative damage [152-156]. More recently, this group showed that citicoline enhances phosphatidylcholine synthesis, which is impaired under ischaemic conditions, attenuating the loss of CTP-phosphocholine cytidyltransferase activity [157-158]. Thus, the drug prevents phospholipid degradation and its downstream effects and promotes the regeneration of cerebral phosphatidylcholine, effects that result in a decreased volume of the cerebral ischaemic lesion [159].

Tornos et al [160] conducted a pharmacological study on the protective effects of citicoline against toxicity in an experimental model of hypoxia induced by potassium cyanide. They found that treatment with oral citicoline for 4 days before hypoxia induction had a protective effect, as demonstrated by a longer survival time in treated animals. These benefits of citicoline may also be ascribed to the activation of cerebral energy metabolism [161] and the increased activity of mitochondrial cytochrome oxidase [162] induced by this drug.

Narumi and Nagaoka [163] investigated the effects of citicoline administration on the metabolism of cerebral monoamines in two rat models of global cerebral ischaemia. In the first model, they performed cerebral ischaemia using bilateral carotid occlusion for 30 minutes in spontaneously hypertensive rats and noted that a significant de

Figure 3. Effect of citicoline on arachidonic acid release in ischaemic rat brains. Citicoline (200 and 1,000 mg i.p.) was administered 10 min before decapitation. Five minutes later, free fatty acids were extracted. Arachidonic acid levels were determined by gas chromatography. [a] $p < 0.05$; [b] $p < 0.001$ vs. untreated ischaemia.

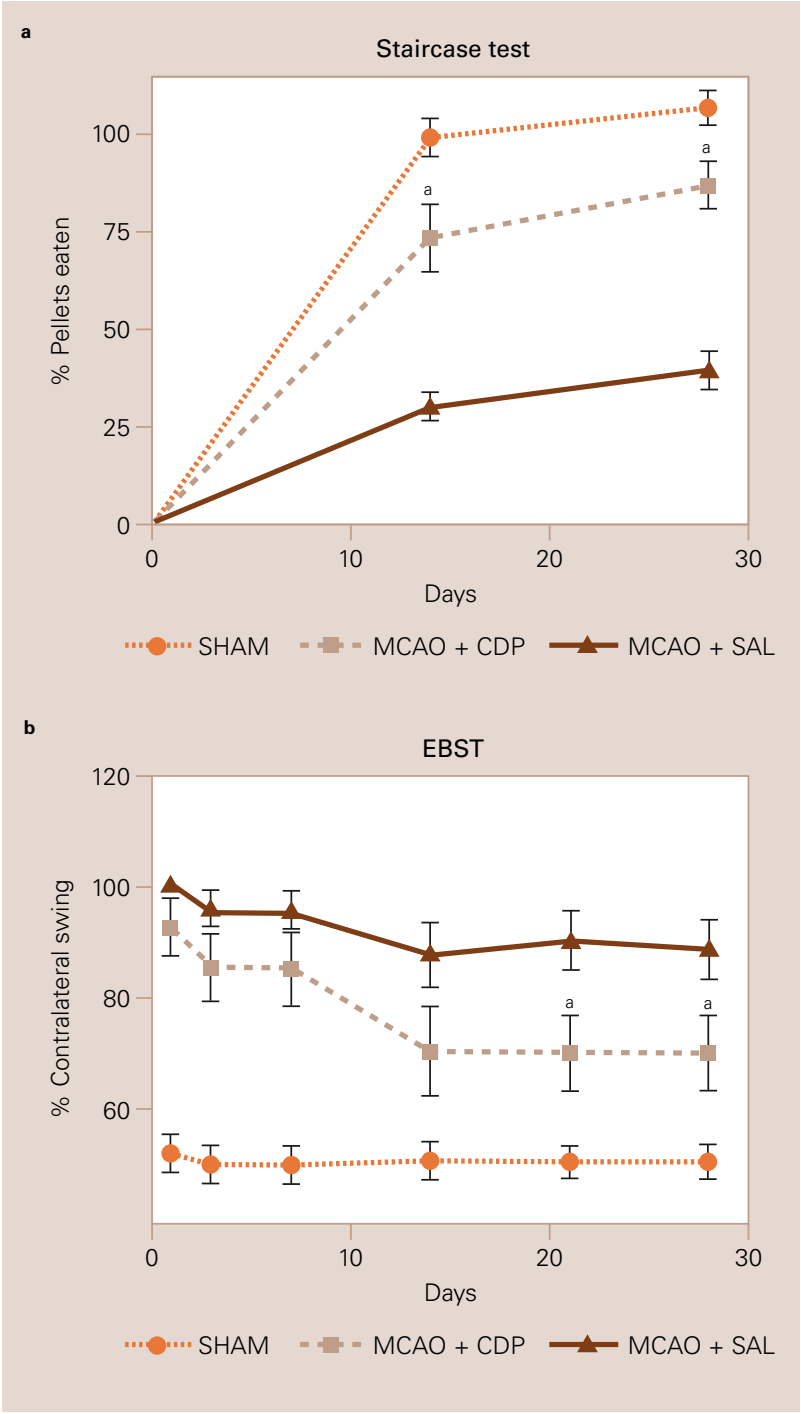


crease in norepinephrine levels occurred in the brain cortex. In this model, the administration of 1,000 mg/kg of citicoline decreased the dopamine levels in the striatum and diencephalon, normalising the decrease in the dopamine metabolites/dopamine ratio induced by ischaemia. In the second model, bilateral carotid occlusion was performed 24 hours after electrocauterisation of both vertebral arteries in Wistar rats. In this model, norepinephrine, dopamine and serotonin levels decreased 70-80% in the brain cortex. Similar decreases were seen for norepinephrine and serotonin levels in the hippocampus, dopamine levels in the nucleus accumbens, dopamine and serotonin levels in the striatum and norepinephrine levels in the diencephalon and brain stem. The administration of 500 mg/kg citicoline significantly enhanced the ischaemia-induced decrease in striatal dopamine levels. Therefore, these authors suggested that citicoline restores dopamine turnover in the striatum of rats subjected to experimental cerebral ischaemia.

Nagai and Nagaoka [164] reported the results of a study investigating the effects of citicoline on glucose uptake in different brain areas from rats with global cerebral ischaemia induced by the occlusion of both carotid arteries for 30 minutes after electrocauterisation of both vertebral arteries. Glucose uptake by the brain was measured four days after recirculation. Without citicoline administration, global cerebral uptake was reduced to 81% of the normal value. After the administration of 250 mg/kg i.p. citicoline twice daily for 3 days after the start of recirculation, the postischaemic reduction in glucose uptake was significantly lower in the brain cortex. This finding suggests that citicoline improves energy metabolism in the brain under ischaemic conditions.

Hurtado et al [165] showed that the administration of citicoline significantly increased brain ATP levels in both healthy and ischaemic animals. This increase in ATP was correlated with a positive effect on glutamate transporters by restoring their normal activity and thereby decreasing both brain parenchymal and circulating glutamate levels. This increase in ATP was correlated with a decreased cerebral infarct volume. These authors demonstrated that citicoline redistributes the glutamate

Figure 4. Effect of chronic treatment with CDP-choline on functional recovery, as determined as sensorimotor integration (a) and asymmetrical motor behaviour (b). CDP-choline (MCAO+CDP) or saline (MCAO+SAL) were administered 24 h after pMCAO and for 28 days following pMCAO. Sensorimotor integration and asymmetrical motor behaviour were studied by the staircase skilled reaching test and the elevated body swing test (EBST), respectively. Data are means ± SEM, $n = 16$. [a] $p < 0.05$ vs. MCAO+SAL.



transporter EAAT2 to lipid raft microdomains and improves glutamate uptake, an effect that is also found after experimental stroke when citicoline is administered 4 h after the ischaemic occlusion [166]. Another study [167] found that chronic treatment with citicoline, initiated 24 h after insult, increases neuronal plasticity within non-injured and functionally connected brain regions and promotes functional recovery. To assess functional recovery, they performed the staircase reaching test and elevated body swing test (EBST) to study sensorimotor integration and asymmetrical motor function, respectively. Treatment with citicoline, initiated 24 h after middle cerebral artery occlusion (MCAO) and maintained for 28 days, improved the functional outcomes of the staircase test (MCAO + CDP = 87.0 ± 6.6% pellets eaten vs. MCAO + SAL = 40.0 ± 4.5%; $p < 0.05$) and the EBST (MCAO + CDP = 70.0 ± 6.8% vs. MCAO + SAL = 88.0 ± 5.4%; contralateral swing $p < 0.05$). In addition, to study potential neuronal substrates of this improved function, we examined the dendritic morphology of layer V pyramidal cells in the undamaged motor cortex using a Golgi-Cox procedure. The animals treated with citicoline showed increased dendritic complexity and spine density compared with the saline group. Zhao et al [168] also showed a positive effect of citicoline on the spatial learning and memory of rats after focal cerebral ischaemia.

Kakihana et al [169] investigated the distribution of labelled citicoline and its effects on acetylcholine synthesis from glucose in the brain cortex of rats subjected to 30 minutes of ischaemia followed by reperfusion. Treatment with citicoline improved glucose metabolism and significantly restored acetylcholine synthesis from glucose. These authors concluded that citicoline improves brain energy metabolism in ischaemic conditions. They [170] subsequently evaluated the effects of citicoline on neurological sequelae and glucose metabolism in the brain in an experimental rat model of transient cerebral ischaemia, showing that high doses of citicoline improved the neurological state of animals subjected to ischaemia, which was correlated to improved brain energy metabolism and drug incorporation in the fraction of membrane phospholipids. These results agree with those obtained in a preliminary study by Fukuda et al [171].

Nagaoka [172] studied the effects of citicoline on stroke onset and mortality in spontaneously hypertensive rats subjected to cerebral ischaemia. Occluding both common carotid arteries induced ischaemia. Citicoline (200-1,000 mg/kg i.p.) admin-

istered before ischaemia induction caused a dose-dependent delay in the onset of stroke and respiratory arrest. These effects were also seen in animals treated after ischaemia induction. In addition, 500 mg/kg i.p. citicoline improved the neurological status of rats undergoing brain ischaemia for 40 minutes followed by reperfusion. These results suggest that citicoline plays a neuroprotective role against cerebral ischaemia and reperfusion.

Saligaut and Boismare [173] studied the effects of citicoline administered at a dose of 1,000 mg/kg per os (p.o.) in Wistar rats undergoing acute hypobaric hypoxia (15 minutes at a simulated altitude of 7,180 meters) by assessing a behaviour-conditioning test, striatal dopamine uptake and levels of dopamine and its metabolites in the striatum. In the behaviour-conditioning test, citicoline protected against hypobaric hypoxia in a different way and to a greater extent than apomorphine. Biochemical studies have shown a presynaptic effect that induced changes in dopamine uptake and improved dopamine release, which are likely due to the activation of tyrosine hydroxylase. Other teams found that citicoline exerted similar effects on tyrosine hydroxylase activity [174].

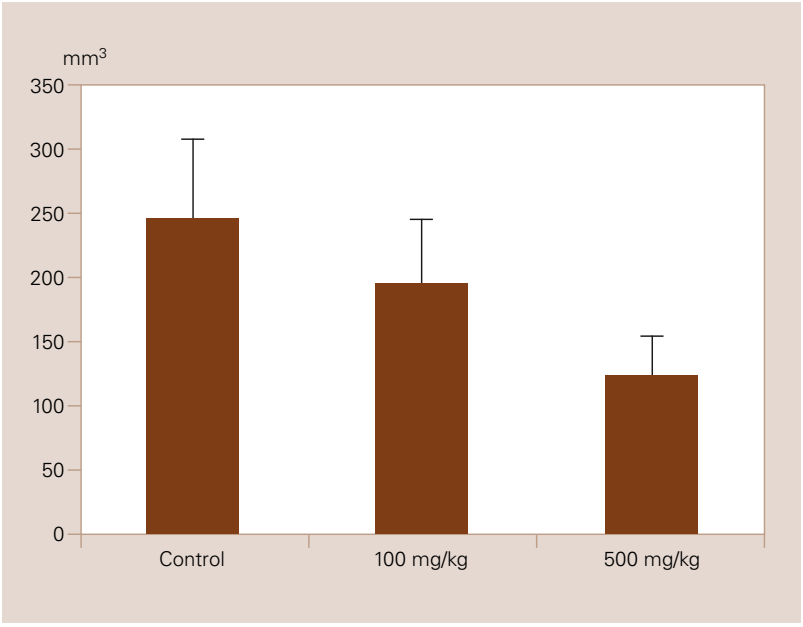
LePoncin-Lafitte et al [97] studied the effects of citicoline on various histological brain changes in an experimental model of multifocal cerebral ischaemia in cats, in which introducing calibrated microspheres into the internal carotid artery caused an ischaemic lesion. Calibrated microspheres produce cerebral microinfarctions that are characterised by a central necrosis area surrounded by a penumbra area and also cause oedema due to rupture of the blood-brain barrier. Citicoline administration decreased the number of lesions and the amount of extravasated albumin considerably, which confirms these authors' hypothesis that citicoline exerts its neuroprotective effects against ischaemia by acting on cell membranes. Araki et al [175] also found some neuroprotective effects of citicoline in complete cerebral ischaemia induced by decapitation and potassium cyanide poisoning in mice.

Aronowski et al [176] evaluated the effects of chronic citicoline administration (500 mg/kg) on recovery in spontaneously hypertensive rats undergoing occlusion of the middle cerebral artery for 30-120 minutes. Either drug or saline was administered intraperitoneally, starting 15 minutes after ischaemia induction and continuing for 14 days. Morphological lesions and neurological disorders (motor and sensorimotor capacities) were analysed by measuring the maximum morphological lesion volume, maximum neurological change and ischaemia duration causing half of the maximum morphological lesion or maximum neurological change. The maximum morphological lesion volume was not affected by citicoline (101.6 ± 11.4 mm^3 for citicoline, 103.3 ± 13.6 mm^3 for saline); however, citicoline significantly increased the ischaemia duration required to cause half of the morphological lesion, which changed from 38.3 ± 5.9 to 60.5 ± 4.3 min ($p < 0.05$). Similarly, citicoline did not change the value of the maximum neurological change (8.5 ± 0.7 for citicoline, 10.1 ± 4.0 for control), but it did significantly increase the ischaemia duration required to cause half of the maximum neurological change from 41.9 ± 4.6 to 72.9 ± 24.5 min ($p < 0.05$). According to these authors, citicoline has greater efficacy in animals that experience a submaximal lesion, which occurred with 30-75 minutes of ischaemia in this model.

Schäbitz et al [177] evaluated the effects of long-term treatment with citicoline in a model of transient focal ischaemia (2 hours) in rats. Ten animals were randomly assigned to each group: placebo (saline 0.3 ml/d/7 d), low dose (citicoline 100 mg/kg/d/7 d i.p.) and high dose (500 mg/Kg/d/7 d i.p.). Treatment was started at the time of reperfusion, after the 2-hour ischaemia period had ended. Daily neurological assessments were made (modified Zea Longa scale), and surviving animals were sacrificed on day 7, after which cerebral oedema and infarct volume were calculated. No differences were seen in the neurological assessments of animals at the end of the study, but a more favourable trend in them was noted in the citicoline high-dose group. The mean infarct volume (Figure 5) was 243.5 ± 88.6 mm^3 in the placebo group, 200.2 ± 19.9 mm^3 in the low-dose group and 125.5 ± 45.2 mm^3 in the high-dose group. These differences were statistically significant ($p < 0.01$). A dose-dependent decrease in cerebral oedema volume was also observed, but the decrease did not reach statistical significance.

In a series of studies, citicoline was shown to have a synergistic effect with other drugs, including thrombolytic [178-181] and neuroprotective drugs [182-185], in the treatment of cerebral ischaemia. Andersen et al [178] conducted an experimental study in a rat model of carotid embolism to evaluate the effects of different doses of citicoline, administered alone or combined with recombinant tissue plasminogen activator (rTPA), on infarct size. Ninety Sprague-Dawley rats that were subjected to embolism in the carotid territory were randomised into 6 groups: (1) saline-treated ani-

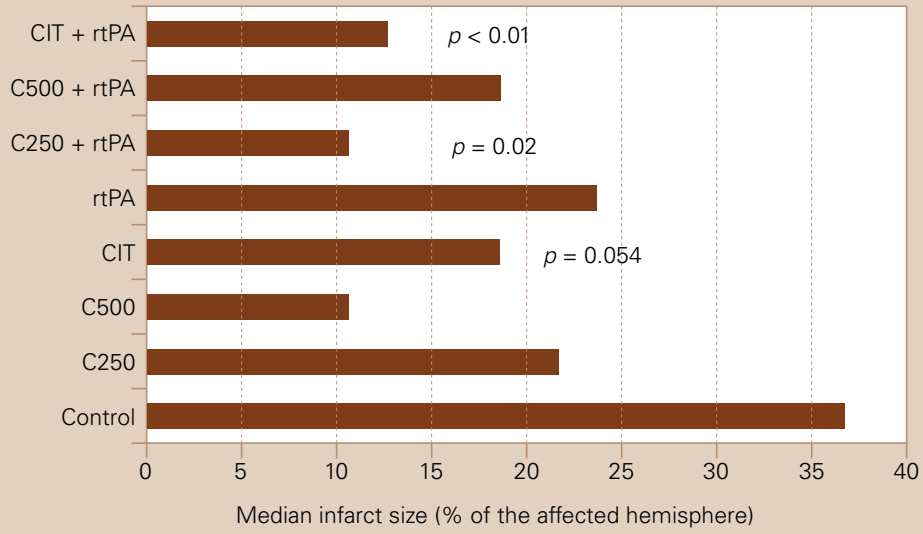
Figure 5. Effect of citicoline at a low dose (100 mg/kg) or high dose (500 mg/kg) on infarct volume. The values represent the mean ± SD. The infarct volume was significantly smaller ($p < 0.01$) in the high-dose citicoline group than in the control group.



mals, (2) citicoline 250 mg/kg, (3) citicoline 500 mg/kg, (4) rTPA 5 mg/kg, (5) rTPA 5 mg/kg + citicoline 250 mg/kg and (6) rTPA5 mg/kg + citicoline 500 mg/kg. Treatment with rTPA was given at a suboptimal dosage (5 mg/kg infused over 45 minutes, starting treatment 45 minutes after embolisation). Citicoline was administered i.p. daily for 4 days. Brains from surviving animals were fixed at four days, and the infarct volume, calculated as a percentage of the total volume of the affected hemisphere, was measured using a microscope. The mean infarct volume values suggested that high-dose citicoline and the combination of citicoline with rTPA decreased the sizes of ischaemic lesions (Figure 6). In the control group, the mean infarct volume was 41.2% (5.9-87.0%). In groups treated with citicoline alone, the values were 30.4% (1.0-70.0%, n.s.) for group 2 and 22.2% (0.7-76.6%, $p < 0.05$) for group 3. With rTPA alone (group 4), the mean volume was 24.5% (1.4-71.1%, n.s.), whereas with combined treatment, the mean volumes were 13.5% (0.2-47.8%, $p = 0.002$) for group 5 and 29.2% (0.11-72.1%, n.s.) for group 6. This study showed that high-dose citicoline and a combination of citicoline at lower doses with rTPA significantly reduced the sizes of brain infarcts. Díez-Tejedor et al [179-180] reported similar results, stating that the results of this association are improved when citicoline is administered immediately after rTPA administration. Shuaib et al [181] investigated the neuroprotective effects of citicoline alone or combined with urokinase in a rat model of focal cerebral ischaemia induced by embolisation at the origin of the middle cerebral artery. Both drugs were administered 2 hours after ischaemia induction. Animals were killed at 72 hours. In saline-treated animals, the infarct volume was 33.1 ± 9.7%. The citicoline-treated animals were divided into two groups: one group was given a single dose of citicoline 300 mg/kg i.p., and the other group received a daily dose of 300 mg/kg i.p. for 3 days. A significant reduction in infarct volume was seen in both groups (20.9 ± 9.7% with a single dose, $p = 0.01$; 18.9 ± 11.4% with multiple doses, $p = 0.008$). The animals treated with urokinase alone, at doses of 5,000 IU/kg, had a smaller infarct volume (19.5 ± 12.5%, $p = 0.01$); however, the greatest volume reduction was achieved in the group of animals treated with the combination of citicoline and urokinase (13.6 ± 9.1%, $p = 0.0002$). These authors concluded that citicoline provides a significant neuroprotective effect that may be enhanced by association with a thrombolytic. Synergistic effects have also been shown between citicoline and MK-801 (dizocilpine) [182], basic fibroblast growth factor (bFGF) [183], lamotrigine [184] and nimodipine [185,186] in models of cerebral ischaemia. It has been demonstrated that citicoline with hypothermia is more effective than either condition alone in ameliorating cerebral damage after transient focal ischaemia [187]. In addition, citicoline and the administration of mesenchymal stem cells show equal efficacy in neurological recovery, decreasing neuronal death and increasing neuronal repair in a model of cerebral infarction in rats, but the combined treatment does not increase the benefit [188].

Fresta et al conducted a series of experiments in models of transient cerebral ischaemia in rats using liposomal citicoline. This study showed significantly increased survival of animals treated with this citicoline formulation [189-191]; more recently, they showed that this same drug formulation significantly reduces the maturation phenomenon (i.e., a delayed cerebral neurodegenerative lesion that occurs after an ischaemic event and results in a significant improvement in brain function) [192]. These results agree with previously discussed results [159] showing that the administration of li-

Figure 6. Effect of the association of citicoline (CIT) and rtPA on infarct size in a model of embolic stroke in rats. C250: citicoline 250 mg/kg; C500: citicoline 500 mg/kg; rtPA: rtPA, 5 mg/kg.



posomal citicoline is more effective than non-liposomal citicoline.

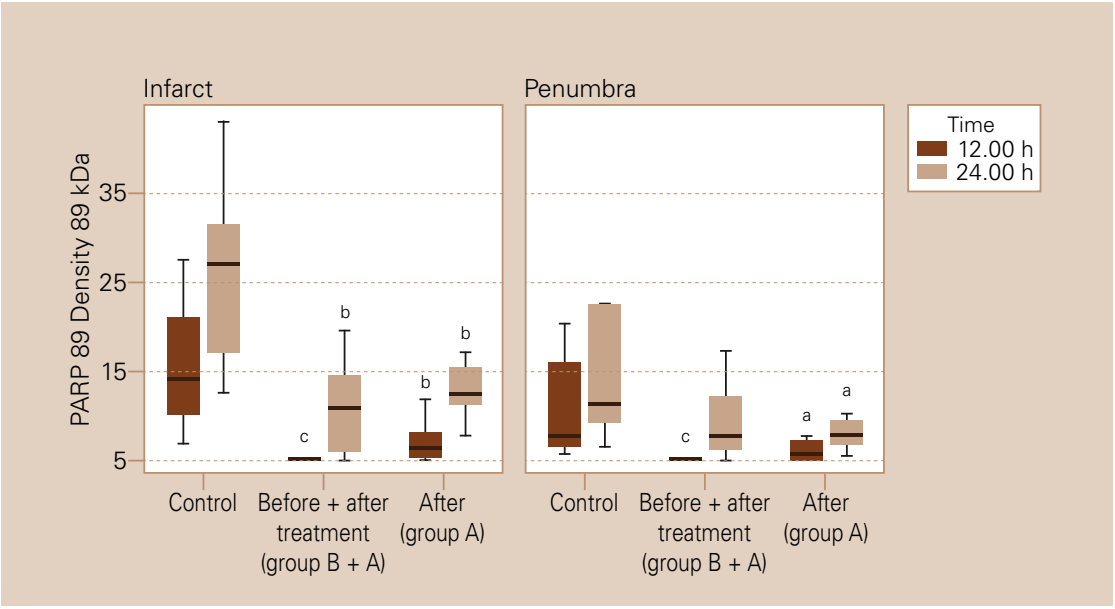
Citicoline also has a neuroprotective effect against neurotoxic damage induced by kainic acid in retinal cells [193-196].

Hamdorf et al [197] exposed 48 rats to a decreasing amount of oxygen for 103 days, i.e., they were exposed to chronic hypoxia. Citicoline showed a protective effect by increasing vigilance under moderate hypoxic conditions (15% O_2). In a subsequent study, these authors [198] analysed the effects of citicoline in Wistar rats subjected to hypoxia for 5 months. Behavioural changes induced by hypoxia were attenuated in the group of animals treated with citicoline. Interestingly, the therapeutic administration of citicoline was more effective than prophylactic administration. In addition, under extreme hypoxia conditions, citicoline showed a protective effect by lengthening survival times. Lee et al [199] demonstrated that citicoline protects against cognitive impairment in a rat model of chronic cerebral hypoperfusion.

However, Masi et al [200] showed that citicoline has certain antiplatelet aggregant effects, which may provide an additional benefit for the treatment of cerebral vascular disease. Pinardi et al [201] investigated the effects of citicoline infusion in Sprague-Dawley rats on relaxation induced by exogenous acetylcholine in the isolated external carotid vascular bed, which has no cholinergic nerve supply, and the isolated internal carotid vascular bed, which has an abundant cholinergic nerve supply. Changes in perfusion pressure were measured during a dose-response curve to acetylcholine and following an infusion of 1 mg/min/30 min of citicoline. The authors noted that citicoline caused relaxation in both vascular beds, which suggests the presence of muscarinic receptors. In the internal carotid vascular bed, citicoline infusion for 30 minutes significantly shifted the dose-response curve to acetylcholine to the left, increasing relaxation. However, this effect did not occur in the external carotid bed. The effect of citicoline was masked when it was jointly infused with hemicolinium. According to these authors, these results suggest that citicoline acts by increasing choline levels at cholinergic endings, increasing acetylcholine synthesis and/or release.

Clark et al [202] examined whether citicoline was able to reduce ischaemic damage and improve

Figure 7. Band densitometry analysis for PARP by western blotting in different groups of rats in the infarct zone and penumbra zone 12 and 24 h after ischaemia. [a] $p < 0.05$; [b] $p < 0.025$; [c] $p < 0.0001$.



functional neurological results in an intracerebral haemorrhage model in mice. They caused haemorrhage in 68 Swiss albino mice by injecting collagenase at the caudate nucleus. Animals randomly received saline or 500 mg/kg i.p. citicoline before the administration of collagenase and at 24 and 48 hours. Mice were assessed using a 28-item neurological scale and were sacrificed at 54 weeks to assess haematoma volume, total damage and surrounding ischaemic damage. With regard to the neurological course, citicoline-treated animals had a better score than placebo-treated animals (10.4 ± 2.0 vs. 12.1 ± 2.4; $p < 0.01$). No differences were observed in haematoma volumes, but a significant reduction in the volume of the surrounding ischaemic damage was noted in animals treated with citicoline (13.8 ± 5.8 mm^3; 10.8 ± 4.3% of the hemisphere) compared to the placebo (17.0 ± 7.1 mm^3; 13.3 ± 5.1%) ($p < 0.05$). According to the authors, these results support a potential role of citicoline for the treatment of intracerebral haemorrhage.

Apoptotic mechanisms have been shown to play a primary role in the pathophysiology of cerebral ischaemic damage, both at the experimental level [203-207] and in humans [208,209]. We therefore investigated [210] whether citicoline could influence apoptotic mechanisms following focal cerebral ischaemia. A model of permanent distal occlusion of the middle cerebral artery was used in Sprague-Dawley rats. Animals were randomised into 4 groups: B + A, citicoline 500 mg/kg i.p. 24 and 1 hour before occlusion and 23 hours after occlusion; A, citicoline 500 mg/kg i.p. within 30 minutes and 23 hours following occlusion; C, saline solution i.p.; D, sham-operated. Animals were killed at 12 (7 animals per group) and 24 hours (7 animals per group) following occlusion. Immunohistochemistry for procaspases 1, 2, 3, 6 and 8 was performed using goat polyclonal antibodies. Using gel electrophoresis and western blotting, specific substrates for caspase action were tested using poly-ADP-ribose polymerase (PARP) antibodies. Ischaemia induced the expression of all procaspases and PARP in both the infarct and penumbra areas 12 and 24 hours following ischaemia. Citicoline reduced the expression levels of all procaspases at 12 and 24 hours following ischaemia, except for procaspase 3 at 24 hours in group A and PARP expression (Figure 7), and the results were more evident in group B + A, suggesting a prophylactic role of citicoline. Citicoline has recently been shown to

inhibit certain intracellular signals involved in apoptotic processes [211] and to maintain these inhibitory effects in different experimental models to study apoptotic mechanisms [128,187,212-216].

Fiedorowicz et al [217] found that citicoline can attenuate brain damage in a rat model of birth asphyxia.

Giralt et al demonstrated that meta-analysis provides an effective technique for aggregating data from experimental stroke studies. With this technique, they confirmed that citicoline reduces the infarct volume and improves outcomes [218], pointing to doses of 300-500 mg/kg as the optimal doses to be translated into a candidate neuroprotective drug for human stroke [219].

According to Drago et al [220], citicoline is a drug of choice for the treatment of cerebrovascular diseases, particularly in its chronic form, because its clinical use is justified by the pharmacological actions that it exerts on the central nervous system. To summarise, citicoline (Figure 8) interferes positively with brain energy metabolism, stimulates central neurotransmission, activates cell repair mechanisms, decreases ischaemic lesion size, inhibits apoptosis associated with ischaemia and has synergistic effects with thrombolytic and neuroprotective drugs.

These characteristics provide citicoline with a suitable pharmacological profile for the treatment of cerebral ischaemia [34,25,221,222]. In addition, a role has been proposed for citicoline in the treatment of complications of infectious diseases such as cerebral malaria [223].

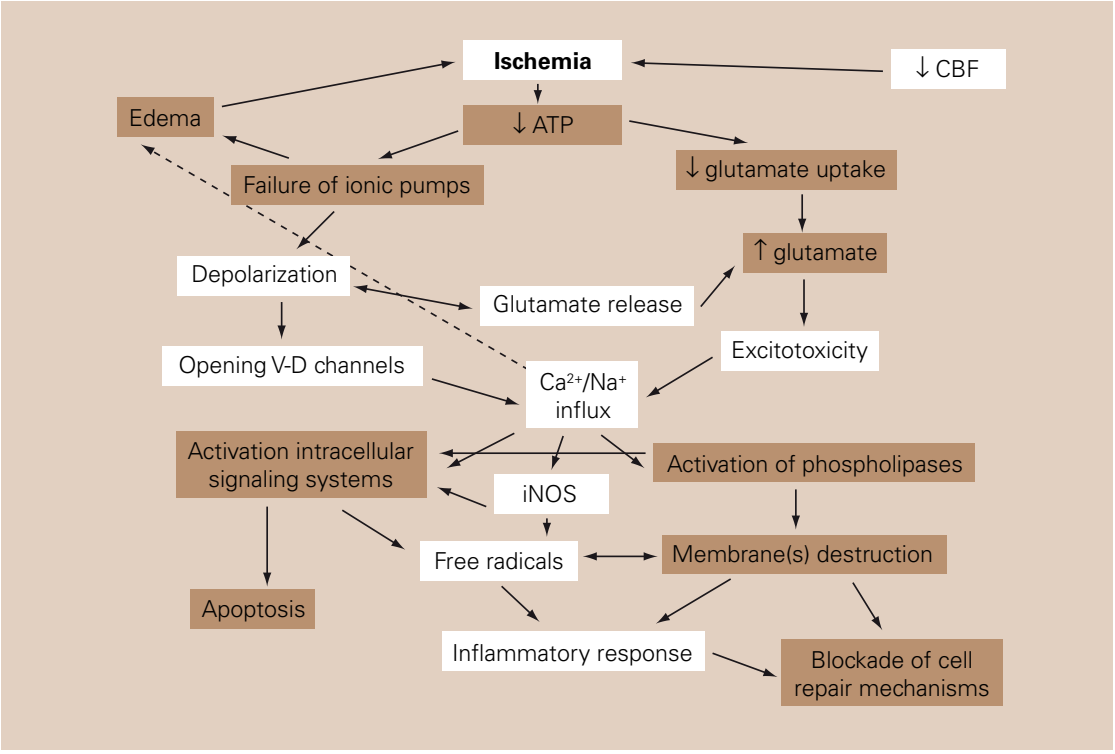
Synaptic transmission and neurotransmitter levels

As discussed previously, citicoline exerts some of its effects through its action on certain neurotransmitters. This section discusses these specific effects on neurotransmission. Most studies have focused on analysing the effects of citicoline on central dopaminergic transmission.

Martinet et al [224] assessed the effects of citicoline administration on norepinephrine, dopamine and serotonin levels in different regions of the rat brain. For this study, conversion of ^{3}H-tyrosine and ^{3}H-tryptophan, administered intravenously, into ^{3}H-norepinephrine, ^{3}H-dopamine and ^{3}H-serotonin was measured. The results obtained with saline administration and those obtained after citicoline administration at different doses were compared. The metabolism of each neurotransmitter was studied in the brain regions in which it has functional activity. Thus, for catecholamines, citicoline action was studied in the striate body, brain cortex and midbrain, whereas for serotonin, the same areas were studies plus hypothalamus. The synthesis rates of dopamine, norepinephrine and serotonin were expressed as conversion indices equal to the ratio between the amount of labelled neurotransmitter per gram of brain (cpm/g) and the tyrosine- or tryptophan-specific radioactivity (cpm/mmol) in the brain. As shown in Figure 9, citicoline significantly increased the levels and the synthesis rate of dopamine in the striate body. The effect exerted on tyrosine levels was very similar. Norepinephrine levels were increased in the cortex but showed no changes compared to the control in the brain stem. With regard to the effects on serotonin, the drug caused decreases in the levels and synthesis rate of this neurotransmitter in the brain stem and hypothalamus, but no changes were seen in the cortex or striatum. According to these authors, increased dopamine synthesis could be attributed to a citicoline-related increase in tyrosine hydroxylase activity, the rate-limiting step in dopamine synthesis. This activation of tyrosine hydroxylase leads to an inhibition of dopamine reuptake at the synapse, an activity that has been shown in *ex vivo* studies [225,226]. In contrast, the increase in dopamine synthesis does not appear to be related to increased levels of tyrosine because increased levels completely saturate tyrosine hydroxylase under physiological conditions. The effects of citicoline on striatal dopamine synthesis are particularly interesting because changes in dopamine synthesis by extrapyramidal dopaminergic neurons are the origins of Parkinson's disease.

Saligaut et al [227] obtained results in agreement with previous results when studying dopamine reuptake in synaptosomes taken from the striate body of rats previously treated with citicoline. Following long-term treatment with this drug, decreased dopamine reuptake by synaptosomes was seen, and the authors related this fact to the increase in tyrosine hydroxylase activity, which involves increased dopamine synthesis. They believe that a structural change in neuronal membranes, mainly at the phospholipid level, could be one of the factors responsible for the change in synaptosomal reuptake of dopamine induced by citicoline. Hypobaric hypoxia was also seen to antagonise the inhibitory effect of citicoline on dopamine reuptake by synaptosomes. This antagonism may be explained by the fact that hypoxia decreases the activity of tyrosine hydroxylase, an enzyme that requires oxygen, counteracting the enzyme activation exerted by citicoline. This leads to decreased

Figure 8. Ischaemic cascade. Darkest boxes show the processes where citicoline has demonstrated pharmacological effects.



dopamine synthesis and a subsequent increase in dopamine reuptake. These authors studied citicoline action in experimental oxotremorine-induced cholinergic syndrome in mice [228] and showed that citicoline pretreatment does not potentiate this syndrome but inhibits salivation induced by oxotremorine. Levodopa antagonises brain symptoms such as the tremor-akinesia induced by oxotremorine. However, this antagonism disappeared in animals under long-term oral treatment with citicoline, confirming the action of citicoline on dopaminergic pathways. The effects of citicoline appear to be mediated by the hypersensitivity of some dopaminergic receptors rather than by a direct stimulating effect on striatal dopaminergic receptors. In another series of experiments, these authors examined the effects of citicoline on catecholamine metabolism in the striatum and hypothalamus from rats subjected to acute hypobaric hypoxia [229]. Their results show that citicoline partially counteracts the effects of hypoxia on the release and metabolism of certain neurotransmitters. In another study, Saligaut et al analysed the effects of citicoline in rats with a unilateral nigrostriatal lesion induced by 6-hydroxydopamine [230]. In damaged animals, amphetamine administration induced ipsiversive circling behaviour, whereas such circling behaviour was contraversive after administration of levodopa and apomorphine. This effect appears to be mediated by the development of a supersensitivity of postsynaptic dopaminergic receptors in the damaged side. Subchronic treatment with citicoline did not induce behavioural effects. Citicoline did not change the stimulating effect of apomorphine but potentiated the effects of levodopa and amphetamine. These data show that the effects of citicoline are mediated by a presynaptic mechanism. Although the potentiation of levodopa may not be explained by the activation of tyrosine hydroxylase, this effect appears to be related to the improved release of dopamine synthesised from exogenous levodopa.

Cansev et al [231] found that peripheral administration of citicoline increases plasma adrenaline and noradrenaline concentrations.

Agut et al [232] indirectly studied the effects of citicoline on dopamine synthesis in the striate body by measuring the local levels of dopamine metabolites in animals in which a blockade of dopaminergic receptors was induced by haloperidol administration. Pretreatment with 100 mg/kg/d/5 d citicoline significantly increased the levels of homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the striatum of treated animals compared to a control group. The increase in the levels of these metabolites was even stronger in a group of animals that also received apomorphine. The results obtained in this study suggest that citicoline increases dopamine synthesis in the striatum of rats in which the activation of such synthesis has been experimentally induced by haloperidol administration. This same investigating team subsequently studied whether citicoline alone, without provoking an increased dopamine demand by dopaminergic receptors, caused increased synthesis of this neurotransmitter, which resulted in increased striatal levels of its main metabolites, HVA and DOPAC [233].

The action of citicoline on the dopaminergic system was also studied by investigating its pharmacological actions in experimental models used for that purpose, hypothermia induced by apomorphine, tardive dyskinesia induced by haloperidol and acrylamide-induced lesions. Agut et al [234] studied the effects of citicoline administration on hypothermia induced by apomorphine, which is considered to be the result of the agonist action of apomorphine on D_2 receptors. In addition to apomorphine, experimental animals received haloperidol at a sufficient dose to partially block apomorphine-induced hypothermia to obtain a pharmacological system that is sensitive to citicoline action on the dopaminergic system. A group of animals received a dose of 100 mg/kg p.o. citicoline, and haloperidol 0.15 mg/kg i.p. was administered at 30 minutes. Thirty minutes later, the rectal temperature was measured, and 1 mg/kg s.c. apomorphine was administered. The rectal temperature was again measured at 30, 60 and 90 minutes. Another group of animals received water instead of citicoline using the same scheme. The effects of the chronic administration of citicoline at a dose of 100 mg/kg/d p.o. for 5 days were also analysed. The same protocol used for acute administration was followed on the last day. Table I shows the mean temperature decrease seen in each animal group and at the different evaluation time points. The acute administration of citicoline causes hypothermia, which is significant for all control time points. Chronic administration only achieves a significant result at 90 minutes. The authors concluded that a 100 mg/kg dose of citicoline, administered acutely by the oral route, has a hypothermising effect that is similar to the effect reported for various dopaminergic agonists. However, they believed that the fact that chronic citicoline administration only caused significant hypothermia at the last time point analysed reflected that, with this form of administration, the tested product predominately acts upon phospholipids rather than upon acetyl-

Figure 9. Influence of citicoline (30 mg/kg i.v.) on catecholamine synthesis at different time points after administration. The graphs show variations in catecholamine concentrations and rates of synthesis, in percentages with respect to the control, at different locations. ● Corpus striatum; ■ Cortex; ▲ Brainstem-mesencephalon; [a] $p < 0.1$, [b] $p < 0.05$; [c] $p < 0.01$.

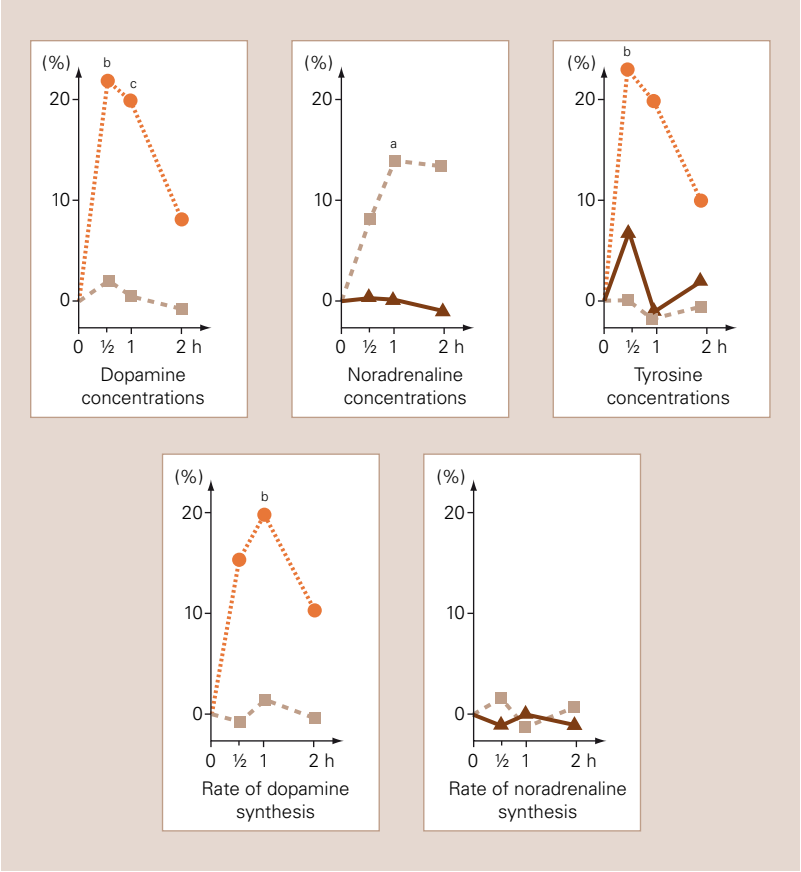


Table I. Decrease in temperature for each batch studied relative to time zero, expressed as the mean for $n = 20$.

Batch	Drugs	Time		
		+ 30 min	+ 60 min	+ 90 min
A	Water (10 mL/kg v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.5 mg/kg i.p.)	1.19 ± 0.23	0.61 ± 0.17	0.19 ± 0.15
B	Citicoline (0.1 g/kg v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.5 mg/kg i.p.)	1.39 ± 0.18 [b]	0.74 ± 0.17 [a]	0.38 ± 0.14 [b]
C	Water (10 mL/kg/5 d v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.5 mg/kg i.p.)	1.13 ± 0.22	0.63 ± 0.25	0.26 ± 0.12
D	Citicoline (0.1 g/kg/5 d v.o.) Apomorphine (1 mg/kg s.c.) Haloperidol (0.15 mg/kg i.p.)	1.11 ± 0.25	0.70 ± 0.19	0.41 ± 0.12 [b]

[a] $p < 0.05$; [b] $p < 0.01$ vs. controls.

choline synthesis. This second pathway of citicoline action would predominate with acute administration, as this would involve relatively rapid utilisation of the choline provided, which would be used for acetylcholine synthesis, increasing tyrosine hydroxylase activity through cholinergic interneurons. In contrast, the chronic administration of citicoline would result in progressively greater availability of cytidine and would therefore divert cerebral choline toward the synthetic pathway of citicoline and phospholipids, which would indirectly result in a dopaminergic agonistic effect. These authors developed an experimental model of tardive dyskinesia induced by haloperidol (2 mg/kg/d/7 d) in rats in a study including the chronic administration of haloperidol or water to a total of 120 animals [235]. Their study found that the administration of citicoline plus apomorphine in rats treated with haloperidol induced a motor activity similar to that seen in the group receiving citicoline alone. The data provided in this study show that, in a model of haloperidol-induced dopaminergic hypersensitivity, oral administration of citicoline induces hypermotility; this administration may induce a phenomenon of competition against other agonists, leading to a partial reduction of the effect of apomorphine in animals pretreated with citicoline. In the model of acrylamide-induced lesion, these authors [236] showed that the administration of low oral doses of citicoline, on the order of 50 mg/kg, is effective to correct the neurological syndrome induced by acrylamide. The simultaneous administration of both substances, which induces obvious weight loss in mice, has also been shown to cause activation of the dopaminergic system, as seen in results obtained with the apomorphine stereotype test.

Shibuya et al [237] measured the striatal dopamine level using fluorometry after the administration of a single dose of 500 mg/kg i.p. citicoline and found that a significant increase occurred in the striatal dopamine level one hour after injection ($p < 0.05$). However, Stanzani [238] showed that citicoline has a neuroprotective effect in the substantia nigra, noting how citicoline protects this area against lesions induced by (horseradish) peroxidases and achieves an increased number of surviving cells. Porceddu and Concas [239] also reported a trophic and/or stimulating effect of citicoline on nigrostriatal dopaminergic neurons in a model of lesions induced by kainic acid. There have also been experimental studies showing protective effects of citicoline in cultures of dopaminergic neurons exposed to 6-hydroxydopamine [240], MPP^+ [241,242] and glutamate [241]. Miwa et al [243] suggested that citicoline may act as a dopamine reuptake inhibitor after administration of a single dose and that this drug may change the activity of dopaminergic neurons through changes in the composition of the neuronal membrane following

repeated doses. In addition, these authors found that citicoline has certain muscarinic effects. Giménez et al [244] showed that chronic administration of citicoline to aged mice promotes partial recovery of the functions of dopaminergic and muscarinic receptors that normally decrease with ageing, and they believe that this action may be explained based on mechanisms involving the fluidity of the neuronal membrane, in agreement with results obtained by Petkov et al [245]. When comparing the effects of citicoline to those of the nootropic drugs adafenoxate and meclofenoxate on the levels of the cerebral biogenic monoamines norepinephrine, dopamine and serotonin in the frontal cortex, striatum, hippocampus and hypothalamus of rats [246], this latter group found that adafenoxate increased norepinephrine levels in the striatum and decreased norepinephrine levels in hypothalamus, increased dopamine levels in the cortex and hypothalamus and decreased these levels in the striatum, and increased serotonin levels in the cortex but decreased these levels in the hippocampus. Meclofenoxate induced decreases in norepinephrine levels in the cortex and hypothalamus, whereas it increased dopamine levels in the hippocampus and hypothalamus and serotonin levels in the cortex, striatum, hippocampus and hypothalamus. The administration of citicoline has also recently been shown to increase dopamine levels in the retina [247]. Citicoline increases norepinephrine levels in the cortex and hypothalamus, dopamine levels in the striatum and serotonin levels in the cortex, striatum and hippocampus, which is a slightly different profile than that seen for nootropic drugs. With regard to the action of citicoline on norepinephrine, a study by López González-Coviella et al [248] showed that citicoline administration increased the total urinary excretion of 3-methoxy-4-hydroxyphenylglycol in rats and humans, reflecting noradrenergic activity and suggesting that citicoline increases norepinephrine release. Recently, citicoline has been experimentally shown to influence the relationship between excitatory (glutamate) and inhibitory (GABA) amino acids in the brain cortex of rats [249]. A series of experiments assessed the potential of citicoline to produce central cholinergic activation. Intracerebroventricular administration of citicoline causes an increase in the levels of vasopressin [250] and other pituitary hormones [251], mainly due to central cholinergic activation. Citicoline has been shown to have a pressor effect in hypotensive animals [252] or in cases of hypotension due to haemorrhagic shock [253,254]. In addition, a contribution of the central histaminergic system is involved in this effect of citicoline [255]. The central cholinergic activating effect exerted by citicoline was again emphasised, and this effect was used to explain the cardiovascular [256-258] and metabolic effects [269-261] of the drug. Ilcol et al [262] observed that citicoline treatment alters serum lipid responses to endotoxins and prevents hepatorenal injury during endotoxemia through a nicotinic acetylcholine receptor-mediated mechanism. Yilmaz et al. [263] showed that citicoline administration restores abnormalities in primary, secondary and tertiary haemostasis and prevents the development of disseminated intravascular coagulation during experimental endotoxemia in dogs, likely by increasing both neuronal and non-neuronal cholinergic activity.

Citicoline also has antinociceptive effects involving the cholinergic system [264,265], opioid and GABA receptors [266] and Na^+/K^+ ATPase activity [267].

To summarise, the effects of citicoline have been studied in experimental models that are used to reveal pharmacological actions on the dopaminergic system. Citicoline has been shown to act as a dopaminergic agonist and has a particularly significant effect on the levels of dopamine and its metabolites in the *corpus striatum*. The results obtained suggest that striatal dopamine synthesis is increased after citicoline administration, probably through tyrosine hydroxylase activation. An increase in dopamine levels would partly result from an inhibition of dopamine reuptake, possibly related to citicoline action on phospholipid synthesis. In addition, citicoline has effects on other monoamines; serotonin and norepinephrine; muscarinic and nicotinic receptors; and glutamate, opioids and GABA.

Learning performance, memory and brain ageing

It has been shown that hypobaric hypoxia decreases learning performance in rats undergoing sound avoidance conditioning and that this effect may be antagonised by pretreatment with apomorphine or other dopaminergic agonists. These effects of hypoxia appear in relation to an inhibition of the metabolism of cerebral catecholamines that would be ultimately responsible for an understimulation of central postsynaptic dopaminergic receptors. Based on these assumptions, Saligaut and Boismare [173] conducted a study on the effects of citicoline administration on learning performance in rats subjected to hypobaric hypoxia. Under hypoxic conditions, citicoline was administered at

300 mg/kg/d for 12 days to a group of rats that underwent learning tests of sound avoidance conditioning in the last 5 days of treatment. The effects seen in this group were compared to those seen in another group receiving apomorphine 0.5 mg/kg 30 minutes before each daily conditioning session and to those recorded in animals receiving both treatments. A group of animals acted as the control and received an ascorbic acid solution under the same experimental conditions. Citicoline partially restored learning performance. The same effect (but to a lesser extent) was seen with apomorphine administration and with the combined administration of both drugs. These results suggest that citicoline administration counteracts, as with dopaminergic agonists, the effects of hypoxia. Previously, we commented on the protective effect of citicoline against the cognitive impairment induced by chronic cerebral hypoperfusion [199].

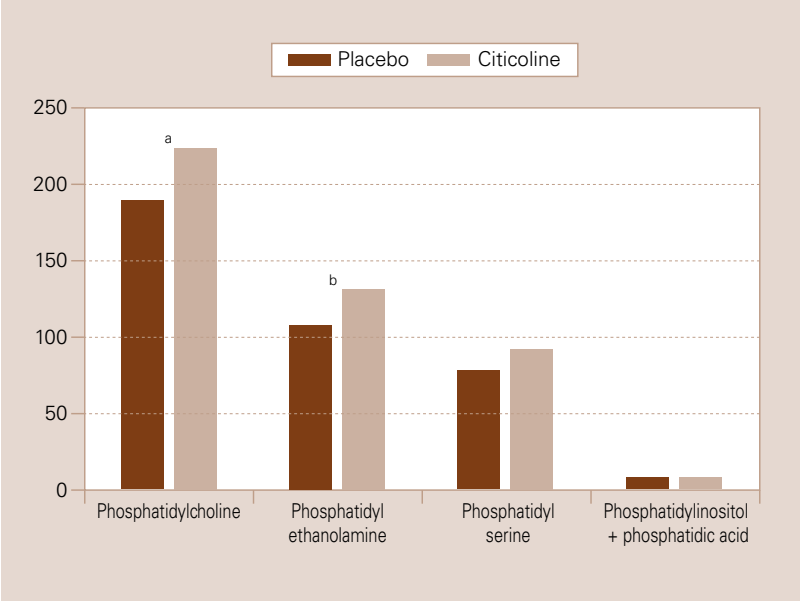
Drago et al [268] administered 10-20 mg/kg/d i.p. citicoline for 20 days to 24-month-old Sprague-Dawley male rats from a strain showing cognitive and motor deficits. The drug was also given to rats with behavioural changes induced by a single injection of scopolamine, a cholinergic antagonist, by prenatal exposure to methylazoxymethanol or by bilateral injections of kainic acid into the magnocellular basal nuclei. In all cases, citicoline improved learning and memory performance, as evaluated using active and passive avoidance tests. In the aged rat group, improved motor capacity and coordination was also observed. For these authors, these results suggest that citicoline affects the central mechanisms involved in cognitive behaviour, probably through a cholinergic action.

Petkov et al [269] showed that citicoline prevents amnesia induced by scopolamine in a model of scopolamine-induced memory impairment. Subsequently, Mosharrof al [270] showed that 100 mg/kg citicoline completely prevented amnesia induced by scopolamine, as did the association of 50 mg/kg citicoline and 500 mg/kg piracetam, which also caused a significant increase in retention. The authors suggested that this effect is mediated by drug actions on neurotransmission. Citicoline acts as a memory-enhancing drug, and this effect is particularly marked in animals with memory deficits [271]. However, Álvarez et al [272] showed that citicoline antagonised amnesia induced by bromazepam in rats. Bruhwyler et al [273] found that chronic administration of citicoline facilitates learning and memory processes in dogs; however, it does not affect the established capacities and, in this model, does not show any effect on the motor, neurovegetative, or motivational systems. According to these authors, this finding represents an argument in favour of the selectivity of drug action in memory processes. Citicoline has even been shown to have a protective effect against mnesic disorders in aged animals [274], in animals in isolation conditions [275], and in spontaneously hypertensive rats when administered as a dietary supplement [276].

There are multiple morphological, neurochemical and physiological changes that characterise brain ageing in mammals. General agreement exists on the existence of age-related changes in certain neurochemical parameters, including enzyme activity, receptor binding and neurotransmission. Biochemical evidence is available for the existence of a component of cholinergic dysfunction and impaired cerebral phospholipid metabolism in the pathophysiology of brain ageing [1,4,5]. De Medio et al [277] investigated the effects of citicoline on changes in lipid metabolism in the brain during ageing. They measured *in vivo* lipid synthesis in different brain areas from 12-month-old male rats. For this experiment, they administered (by injection into the lateral cerebral ventricle) a mixture of (2-^{3}H)glycerol and (Me-^{14}C)choline, as lipid precursors, and measured the incorporation of these precursors into the fractions of total lipids, water-soluble intermediates and choline phospholipids at 1 hour after isotope administration. In another series of experiments, citicoline was injected intraventricularly into aged rats 10 minutes before sacrifice, and the same radioactivity tests as described above were performed. In the studied areas, the distribution of the radioactivity contained in citicoline in the brain 10 minutes following administration showed the enrichment of nucleotides and related water-soluble compounds. The incorporation of labelled glycerol, which is greatly decreased in aged rats, increased in all areas. The incorporation of labelled choline also decreases with ageing, and citicoline increased such incorporation in the cortex. As a result, the ^{3}H/^{14}C ratio was increased in total lipids and in phosphatidylcholine and choline plasmalogens following citicoline treatment. Following this line of study, López González-Coviella et al [278] studied the effects of oral citicoline on the phospholipid content in mouse brains. These authors supplemented the animal diet with 500 mg/kg/d citicoline for 27 months in 3-month-old mice and for 90, 42 and 3 days in 12-month-old mice, after which phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine levels and the contents of phos-

phatidylinositol plus phosphatidic acid were measured in brain cortex. After 27 months of treatment, phosphatidylcholine and phosphatidylethanolamine levels increased significantly, by 19% and 20%, respectively, whereas phosphatidylserine levels increased by 18%, but this change was not statistically significant (Figure 10). Similar increases were noted when 12-month-old animals were treated for 3 months but not with shorter treatment periods. These results suggest that chronic administration of citicoline may have significant effects on the phospholipid composition of the brain that may be partly responsible for the reported therapeutic efficacy of this drug. Wang and Lee [279] obtained similar results in their study. Plataras et al [280] showed that citicoline restores the activity of hippocampal acetylcholinesterase and Na^+/K^+ pumps, indicating that these mechanisms are involved in the improvement of memory performance exerted by citicoline. Giménez et al [281] showed that citicoline, administered for 2 months to aged rats, caused significant activation of cytidine triphosphate:phosphocholine cytidyltransferase, which, according to the authors, would explain the reparative effects of the drug on damaged membranes of aged animals. This same investigating team made a more extensive study of the effects of citicoline on the activity of this enzymatic system and showed that, in addition to its effect on phospholipid metabolism, citicoline has a regulatory effect on platelet-activating factor levels in the brain [282,283]. All of these effects occur with no changes in the plasma levels of homocysteine, a known risk factor [284]. However, citicoline also offers beneficial actions on the brain metabolism of nucleic acids and proteins [279,285-287], on dopaminergic, nicotinic and muscarinic receptors [256], and on neuroendocrine and neurosecretory changes [288-290] in experimental ageing models, as well as a neuroprotective effect against neurotoxic aggressions [291-293], an immunomodulatory effect [294] and an antiapoptotic effect [295] in various neurodegeneration models. Because of such actions, various studies have shown the positive effects of citicoline on learning and memory in aged animals [273,296-298]. Based on these effects and the effects on neuroplasticity [299] and on proliferation and differentiation of astroglial cells [10,300], the use of citicoline in neurodegenerative diseases has been proposed, but there are some exceptions, including the lack of a protective effect of the drug in a model of Huntington's disease [301].

Figure 10. Effect of chronic administration of citicoline on the brain titres of phospholipids in 30-month-old mice fed a dietary supplement with citicoline (500 mg/kg/day) or placebo for 27 months. [a] $p < 0.05$; [b] $p < 0.01$.



Experimental withdrawal syndrome and intoxications

If 300 mg citicoline is injected by the intracarotid route into cats, effects similar to those seen with the administration of 2 mg of morphine by the same route are obtained. The animal shows symptoms of anger and alertness, and the tail is placed in a rigid and upright position. This finding led to the thinking that both substances could have parallel effects on neuroreceptors of endogenous opiates and that citicoline administration could be valuable in opiate withdrawal syndrome by slowing the effects of sudden drug discontinuation [302]. Tornos et al [303] studied the effects of citicoline administration on experimental withdrawal syndrome by analysing various methods, such as the jumping test in mice and studies of behaviour and body temperature changes in rats. The withdrawal syndrome caused by naloxone administration to morphine-dependent mice was assessed based on the number of jumps by the animals. A decrease in severity was seen in the group of animals treated with 2 g/kg p.o. citicoline compared

to the untreated animal group. This decreased severity of the withdrawal syndrome was shown by a 39% decrease in the mean number of jumps by animals within 10 minutes of administration of the opiate antagonist. Similarly, the behavioural study in morphine-dependent rats showed that administration of a 2 g/kg oral dose of citicoline simultaneously with naloxone was able to significantly decrease the severity of manifestations that characterise the withdrawal picture provoked. With regard to hypothermia caused by naloxone administration in morphine-dependent rats, administration of a single oral dose of citicoline almost completely neutralises this effect.

Characteristic histological findings of foetal alcohol syndrome include delayed maturation and late development of dendrites in the neocortex, hippocampus and cerebellum. Based on these data, Patt et al [304] conducted a study to investigate the effects of citicoline on Purkinje cells from newborn rats from alcoholic dams and showed that this stabilising agent of neuronal membranes decreases the harmful effects of alcohol on the central nervous system. Petkov et al [305] showed that citicoline decreases mnesic deficits in rats pre- and postnatally exposed to alcohol, which may be related to the beneficial effects on acetylcholine synthesis and release shown using cerebral microdialysis in rats that were chronically exposed to alcohol [306,307]. Citicoline also has as protective effect in nicotine intoxication [308].

Toxicity

Acute toxicity

Toxicity was studied for single administration of citicoline with different administration routes. in various animal species. The intravenous LD_{50} in mice, rats and rabbits is 4.6, 4.15 and 1.95 g/kg, respectively [309,310]. Oral LD_{50} is 27.14 g/kg in mice and 18.5 g/kg in rats [311]. The intravenous LD_{50} of citicoline is approximately 44 times higher than the LD_{50} of choline hydrochloride at equivalent doses and it has been shown that choline doses inducing cholinergic crises do not cause any signs of toxicity when equivalent doses of citicoline are administered [312,313]. This finding suggests that the administration of choline has metabolic implications that are clearly different from those of exogenous choline administration. The administration of 2,000 mg/kg of citicoline p.o. for 14 days was well tolerated [314].

Subacute toxicity

Intraperitoneal administration of doses up to 2 g/kg/d of citicoline to rats for 4.5 weeks did not result in clinical signs of toxicity or significant changes in the haematological, biochemical, or histological parameters analysed. A slight decrease in intake and weight gain was observed only after 2 weeks of the study [311]. Similar results were seen following subcutaneous administration of up 1 g/kg for 4 weeks to male rats [310]. Oral administration of 1.5 g/kg/d to rats for 30 days did not cause weight, haematological, biochemical or histological changes [315].

Chronic toxicity

Chronic oral (1.5 g/kg/d for 6 months in dogs) and intraperitoneal (1 g/kg/d for 12 weeks in rats) toxicity studies did not reveal significant abnormalities related to drug administration [310,316]. Intravenous administration of 300-500 mg/kg/d citicoline for 3 months in dogs only caused toxic signs immediately after injection, including vomiting and occasional diarrhoea and sialorrhoea [313]. In a 90-day study in rats, 100, 350 and 1,000 mg/kg/day oral doses resulted in no mortality. In males, slight but significant increases in serum creatinine (350 and 1,000 mg/kg/day) and decreases in urine volume (all treated groups) were observed. In females, slight significant increases in total white blood cell and absolute lymphocyte counts (1,000 mg/kg/day) and blood urea nitrogen (BUN) (100 and 350 but not 1,000 mg/kg/day) were noted. A dose-related increase in renal tubular mineralisation, without degenerative or inflammatory reaction, was found in females (all treated groups) and two males (1,000 mg/kg/day). Renal mineralisation in rats (especially females) is influenced by calcium:phosphorus ratios in the diet. A high level of citicoline consumption resulted in increased phosphorus intake in rats and likely explains this result [314].

Teratogenicity

Citicoline was administered to albino rabbits at a dose of 800 mg/kg during the organogenesis phase, i.e., from days 7 to 18 of pregnancy. The animals were sacrificed on day 29, and a detailed examination was made of the foetuses and their mothers. No signs of maternal or embryofoetal toxicity were observed. The effects on organogenesis were imperceptible, and only a slight delay in cranial os-

teogenesis was observed in 10% of treated foetuses (unpublished data).

Pharmacokinetics

Plasma level curves. Bioavailability

Labelled citicoline (methyl ^{14}C) was administered to rats at a dose of 4 mg/kg by jugular vein injection and orally using a nasogastric tube [317]. The results obtained, expressed as the percent radioactivity in 10 mL of blood for each administration route, are shown in Table III. From these data, the ratio between the bioavailability of the oral and the intravenous administration route was estimated and found to be virtually one, which agrees with the fact, demonstrated in the same study, that no residual radioactivity is found in faeces excreted in the 72 hours following oral administration.

López González-Coviella et al [318] studied the effects of citicoline on the plasma levels of cytidine, choline and citicoline in healthy volunteers receiving the drug by the oral or intravenous route and in rats treated by the intravenous route. Two hours following the administration of a single oral dose of 2 g citicoline, choline plasma levels increased 48% and cytidine plasma levels increased 136% (Figure 11). In individuals receiving three 2-g doses at 2-hour intervals, choline plasma levels reached a peak, representing approximately 30% of the baseline value, 4 hours after the administration of the initial citicoline dose, whereas cytidine plasma levels increased for up to 6 hours (Figure 12) and were 5-fold higher than the baseline value ($p < 0.001$). Citicoline administered intravenously was rapidly hydrolysed in humans and rats [319]. In healthy individuals receiving a citicoline infusion of 3 g in 500 mL of physiological saline over 30 minutes, citicoline levels were virtually undetectable immediately after the end of the infusion period, when plasma levels of cytidine and choline reached a peak, although their concentrations remained significantly increased up to 6 hours after the start of the infusion (Figure 13). These observations show that citicoline, administered by both oral and intravenous routes, is converted into two major circulating metabolites, cytidine and choline. However, in humans, plasma cytidine is converted to uridine, its circulating form, which is transformed in the brain to uridine phosphate, which will be converted into cytidine triphosphate at the neuronal level [320].

Table II. Blood kinetics of the total radioactivity of 4 mg/g methyl ^{14}C-citicoline after oral or intravenous administration to male rats. The percentages of radioactivity (mean ± SD) with respect to the total administered are shown.

Time	Oral route	Intravenous route
10 min	0.26 ± 0.12	3.05 ± 0.24
20 min	0.40 ± 0.02	2.59 ± 0.31
30 min	0.74 ± 0.01	1.47 ± 0.22
1 h	1.32 ± 0.40	1.40 ± 0.02
2 h	2.33 ± 0.63	2.84 ± 0.02
3 h	3.31 ± 0.86	2.50 ± 0.05
4 h	3.57 ± 0.88	2.77 ± 1.00
5 h	4.17 ± 0.83	3.37 ± 0.31
6 h	4.18 ± 0.03	3.68 ± 0.02
7 h	3.81 ± 0.73	–
24 h	2.48 ± 0.40	3.12 ± 0.19

Tissue diffusion and distribution. Transport and metabolism

Tissue diffusion of citicoline and its components has been studied in rats that were intravenously administered (methyl ^{14}C, 5-^{3}H) citicoline that was labelled in the choline and the cytidine fractions [321,322]. In the same battery test, plasma radioactivity levels were measured for 30 minutes following administration. Renal and faecal excretion values of labelled metabolites were also measured for 48 hours. As early as 2 minutes following injection, less than 10% of the administered radioactivity was found in the plasma. In addition, the radioactivity excreted by the kidney during the first 48 hours only accounted for 2.5% of the ^{14}C administered and 6.5% of the ^{3}H administered. In the same time interval, faecal excretion did not exceed 2% of the administered dose. These results suggest that citicoline rapidly diffuses to the tissues following administration and is actively used by tissues. Figure 14 shows the radioactivity levels that were found in the liver, brain and kidney at different time points following intravenous administration of dually labelled citicoline. There is a special interest in changes in brain levels of radioactivity. Radioactivity uptake by the brain gradually increases for the

Figure 11. Plasma concentrations of choline and cytidine immediately after administration of a single oral dose of 2 g citicoline in humans.

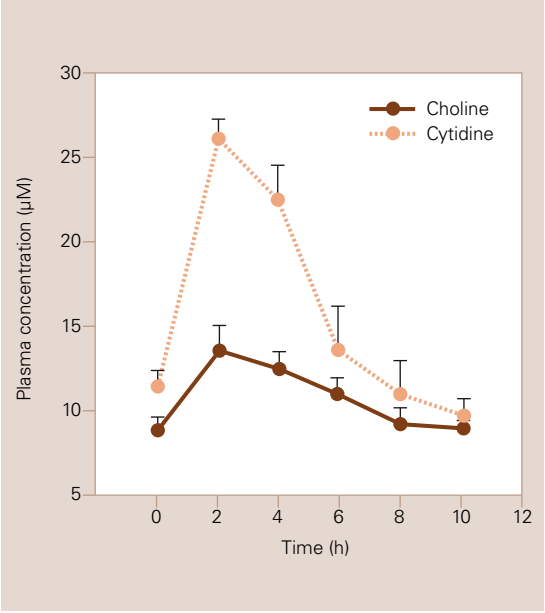
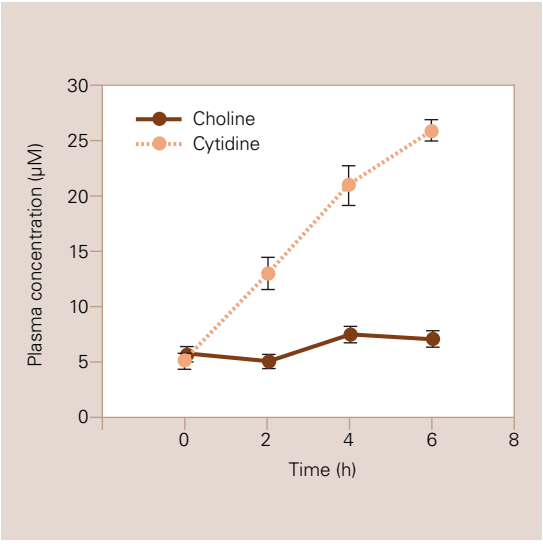


Figure 12. Plasma concentrations of choline and cytidine immediately after administration of three consecutive oral doses (2 g) in humans.



first 10 hours after drug administration, and these levels achieved remain unchanged at 48 hours.

In a group of animals, the radioactivity levels of labelled compounds were measured in the brain at 0.5, 1, 4 and 48 hours after the administration of dually labelled citicoline. Radioactivity corresponding to ^{3}H in the brain was primarily concentrated in cytidine nucleotides at the beginning of the experiment but was subsequently concentrated in nucleic acids. With regard to compounds labelled with ^{14}C, the highest levels initially corresponded to betaine, choline and phosphorylcholine, whereas at 4 hours, ^{14}C-methionine and ^{14}C -phospholipids accounted for 26.4% and 24.2%, respectively, of the total cerebral radioactivity corresponding to ^{14}C. At 48 hours, this radioactivity was primarily concentrated in phospholipids and proteins. Therefore, the levels of labelled phospholipids continuously increased in the 48 hours following the administration of dually labelled citicoline. As shown in Figure 15, this increase is rapid in the first 5 hours but then becomes slower over time.

In another test battery, the presence of the drug in various brain areas and its distribution in cerebral ultrastructures were measured following the administration of (methyl ^{14}C) citicoline [323-327]. In a study performed with high-performance autoradiography in mouse brains, the radioactive marker was widely incorporated into the different cerebral areas studied, including the brain cortex, white matter and central grey nuclei, at 24 hours following the administration of labelled citicoline [323]. It was found in both intra- and extracellular spaces, with a particularly strong presence in cell membranes. In the same experimental model but 10 days following the administration of the labelled drug [324], a concentration of radioactivity was seen in the more myelinated areas, as well as marked uptake by cerebellar Purkinje cells. Using low-performance autoradiography, the distribution of radioactivity of labelled citicoline in rat brains was analysed 5 and 24 hours after drug administration [325]. At 24 hours, most radioactivity was detected at the intracellular level. In another study, the incorporation of radioactivity from (methyl ^{14}C) citicoline after oral administration to male Sprague-Dawley rats was analysed in different cerebral phospholipid fractions [326]. Of the total radioactivity measured in the brain, 62.8% was found to be part of brain phospholipids, particularly phosphatidylcholine and sphingomyelin, showing that citicoline administered by the oral route has an effect on the synthesis of structural phospholip-

Table III. Most significant parameters in the elimination kinetics of ^{14}C-citicoline after oral administration. Data show the means of six individuals.

Parameters	CO_2	Urine	Faeces
Maximum rate of excretion (% dose/h)	1.22 ± 0.59	0.159 ± 0.084	0.021 ± 0.008
Time of maximum excretion (h)	1.60 ± 0.73	1.3 ± 0.8	56 ± 18
First phase of elimination			
Apparent half-life	2.58 ± 0.60	6.62 ± 1.28	–
Apparent rate of elimination (% dose/h)	0.279 ± 0.055	0.107 ± 0.017	–
Second phase of elimination			
Apparent half-life (h)	56.22 ± 33.39	71.08 ± 58.16	19.39 ± 6.63
Apparent rate of elimination (% dose/h)	0.030 ± 0.049	0.013 ± 0.006	0.039 ± 0.014

ids of cell membranes. These results agree with those obtained by Aguilar et al [327], who showed that radioactivity from labelled citicoline is associated with cytoplasmic and mitochondrial membranes in brain homogenate.

In conclusion, these studies show that administered citicoline is widely distributed in brain structures, with a rapid incorporation of the choline fraction into structural phospholipids and of the cytosine fraction into cytidine nucleotides and nucleic acids. Citicoline reaches the brain and actively incorporates into the cytoplasmic and mitochondrial cell membranes, becoming part of the structural phospholipid fraction [319,328,329].

Elimination route and kinetics

When labelled citicoline is administered by either the oral or intravenous route, radioactivity is eliminated very slowly by the urinary or faecal route and in expired CO_2 [330].

Figure 16 shows total radioactivity excretion for 5 days following the oral administration of ^{14}C -citicoline to healthy volunteers. Table III provides the primary data on the elimination kinetics of the compound.

Two phases are differentiated in urinary elimination of the drug: a first phase, lasting approximately 36 hours, in which the excretion rate decreases rapidly, and a second phase, in which the excretion rate decreases much more slowly. The same phenomenon occurs with expired CO_2, whose elimination rate decreases rapidly for approximately the first 15 hours, after which a slower decrease occurs.

Clinical experience

Head injury and sequelae

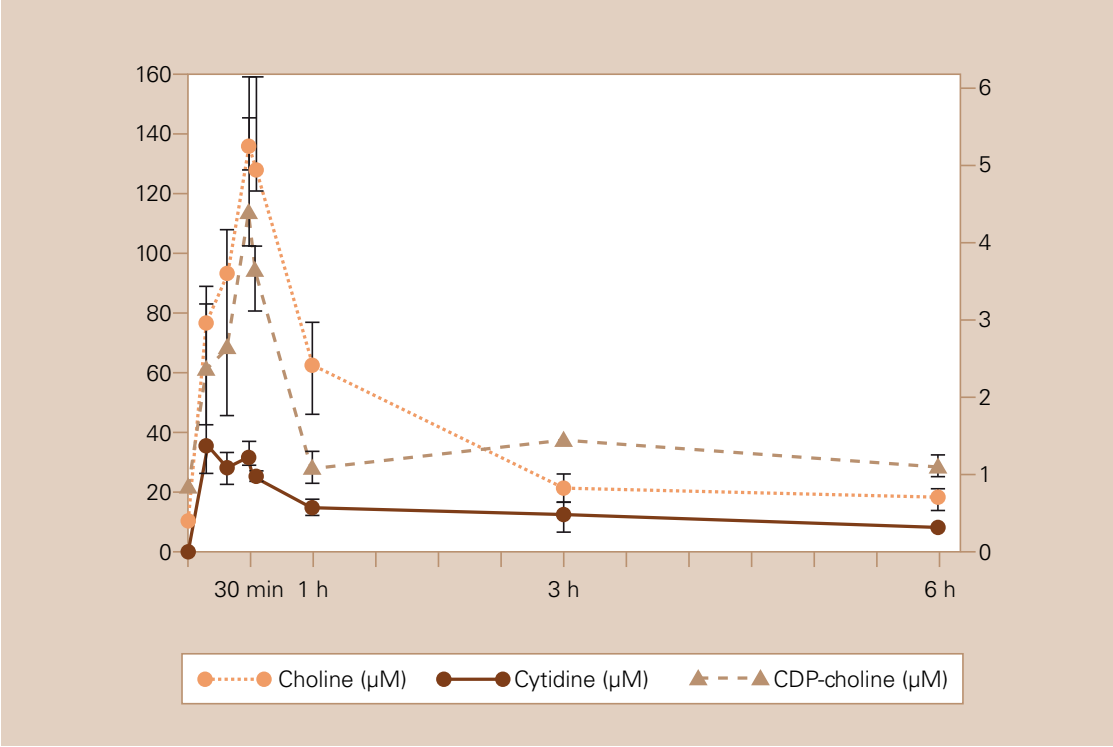
The above-reported experimental studies show that the administration of citicoline leads to a significant regression of brain oedema and improvements in electroencephalographic tracing, impairment of consciousness and survival quality. The effect on consciousness level is attributable to the facilitating action of the electroencephalographic arousal reaction, induced by stimulation of the ascending reticular activating system at the level of the brain stem.

Based on these experimental assumptions, many clinical trials have been conducted to verify whether these effects have implications for the treatment of patients with head injury.

In 1967, Moriyama et al [331] published a study on the effects of citicoline in 25 patients with head injuries and depressed consciousness. The drug was effective, leading to recovery from neurological clinical symptoms and a return to a conscious state in 70% of cases, and was very well tolerated, causing no side effects.

Ayuso and Saiz [332] conducted a double-blind study on the value of citicoline in mnesic dysfunction induced by bilateral electroshock in a series of 22 patients admitted to the hospital for endogenous depression. The group receiving the active drug had a lower reduction in memory performance after four electroshock sessions compared to the control group, showing the value of citicoline for treating patients with memory disorders as result of an injury or lesion.

Figure 13. Concentrations of choline, cytidine and CDP-choline in human plasma after intravenous infusion of a solution of citicoline (3 g/500 mL physiological saline solution).



De la Herrán et al [333] compared the effects of citicoline administration in a series of 50 patients with impaired levels of consciousness (of traumatic origin in 32 cases) to another series of patients with similar characteristics who were receiving standard treatment. Thirty-four percent of patients recovered consciousness within 48 hours. After a few days, 66% of patients had recovered consciousness. These results were better than those achieved in the control group. These results showed that citicoline reactivates and accelerates normalisation of the consciousness stated in patients with head injuries.

Carcassonne and LeTourneau [334] conducted a double-blind study in a series of 43 children with a true consciousness disorder of traumatic origin, after excluding severe cases and cases requiring surgical treatment. After analysing the results, these authors concluded that citicoline is very well tolerated, both locally and systemically: it significantly accelerates the recovery of a normal consciousness state, it accelerates the disappearance of neuropsychological disorders and cerebral electrogenesis disorders and it confers a better quality of the evolution of patients.

Espagno et al [335] compared the effects of citicoline and placebo in a series of 46 patients who had sustained head injuries. The authors conducted a double-blind study in which 22 patients received 250 mg/d citicoline intraperitoneally for 20 days, and 24 patients were given placebo. The results showed that, for patients in mild comas, citicoline significantly accelerated ($p < 0.05$) the recovery of consciousness, whereas for patients in more severe comas and at the administered dose (currently considered to be highly inadequate), citicoline improved the prognosis. In the placebo group, 75.2% of patients showed late recovery (>15 days) of consciousness and/or progressed to death. In contrast, in the group treated with the citicoline, recovery from coma beyond day 15 occurred in 31% of cases and the incidence of prolonged coma

and/or death was 12.5%. In conclusion, citicoline resulted in earlier recovery of consciousness and an increased number of clinical and electroencephalographic improvements and was very well tolerated.

Richer and Cohadon [336] conducted a double-blind study in a group of 60 patients with comas of traumatic origin who were distributed into two homogeneous groups, one of which was given the active drug and the other given a placebo. With regard to coma duration, the number of patients who recovered consciousness at 60 days was significantly greater ($p < 0.01$) in the group treated with citicoline. After 90 days, greater recovery ($p < 0.04$) from motor deficits was observed in the citicoline-treated group. Gait recovery was also significantly accelerated in the active drug group. As a result, greater social and occupational reinsertion was found at 60 days in the group treated with citicoline ($p < 0.06$). This finding demonstrates the limiting effect of the duration of posttraumatic coma of citicoline and its participation in the restoration of deficits related to the brain lesions associated with such comas. There were no changes in mortality associated with the treatments.

In a double-blind trial, Lecuire and Duplay [337] compared the effects of a 750-mg/d intravenous dose of citicoline to those of meclofenoxate at 3 g/d i.v. in a group of 25 patients. There was significant improvement in the patient group treated with citicoline, particularly with respect to the recovery of consciousness, electroencephalographic changes and functional recovery. The mean coma duration was 10 days in the citicoline group, compared to 20 days in the meclofenoxate group. At 10 days, electroencephalographic tracings improved in 50% of the citicoline-treated patients and in 18% of the meclofenoxate-treated patients. Therefore, citicoline was shown to be superior to meclofenoxate, and its main characteristic was accelerated recovery of the consciousness level, which is related to an improvement in electroencephalographic tracing. These same authors carried out an open-label study in a series of 154 patients with head injuries [338]. Their study assessed the effects of citicoline treatment and found that the drug accelerates patient arousal and recovery from deficit syndromes and improves the quality of survival. Lecuire [339] subsequently performed a double-blind study comparing piracetam (6 g/d) vs. citicoline (750 mg/d) in a group of 40 patients who sustained head injuries and found a favourable evolution in 75% of patients in the citicoline group, compared to 33% in the piracetam group.

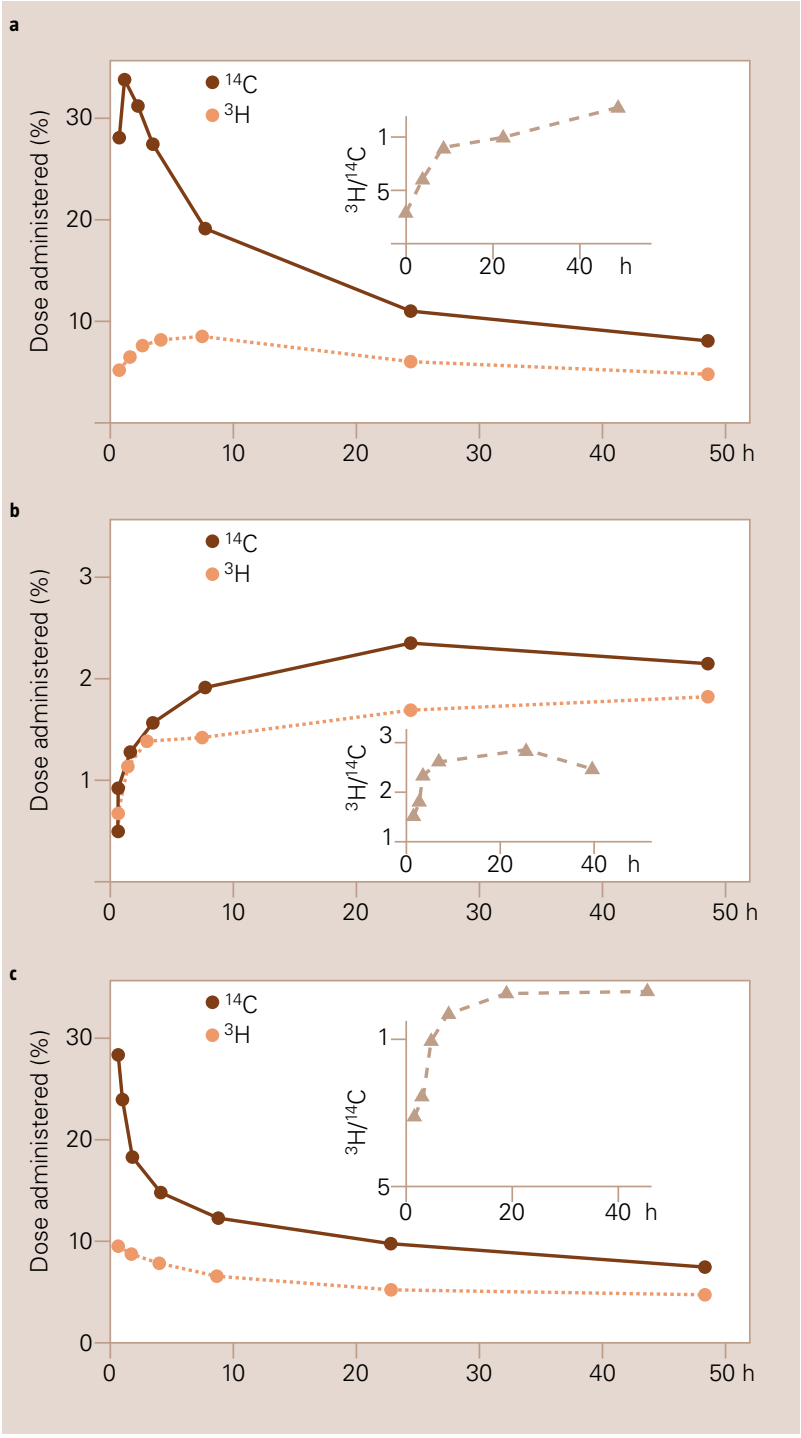
Cohadon et al [16,340] showed the clinical efficacy of citicoline in a double-blind study conducted on a series of 60 patients with severe head injuries. A standard treatment was used in both groups, and surgery was performed when required. One group of patients was given 750 mg/d citicoline intravenously for the first 6 days and by the intramuscular route for an additional 20 days. The other group was administered a placebo. Clinical evaluation was continued up to 6 months. At 15 days, the response to painful stimuli was superior in the group of citicoline-treated patients ($p < 0.01$), and an earlier recovery of consciousness was seen in this group (Figure 17). The authors also noted a greater recovery from neurological deficits in the group having the active treatment. After 120 days, autonomous ambulation was seen in 84% of the patients in the citicoline group, compared to 62.5% of the patients in the placebo group. This difference was statistically significant from day 60 ($p < 0.01$). Table IV shows the final outcomes obtained in both groups, as assessed using the Glasgow Outcome Scale (GOS). The mortality rate was similar in both groups. Data reported in this study show that citicoline shortens the time elapsed to recovery of consciousness and accelerates recovery from neurological deficits in patients with severe head injury.

Deleuze et al [341] reported that citicoline decreases serum creatine phosphokinase (CPK) levels and lactate levels in cerebrospinal fluid (CSF), with a decrease in the lactate/pyruvate ratio, in patients with severe brain distress and coma. They emphasised that the product was very well tolerated.

Ogashiwa et al (102) conducted a clinical trial in 101 patients with consciousness disorders from different causes (20% of traumatic origin) and showed the effectiveness of citicoline for improving the General Recovery Rate, which is closely related to the Principal Component Analysis Score. The authors found that citicoline is more effective in items related to the executive factor than in items related to the verbal factor and that the greatest effect was achieved in patients under 60 years of age and with a stabilised period of impaired consciousness of no longer than 3 weeks. They emphasised the excellent tolerability of the product and even administered it by the intrathecal route in some cases [342,343].

At the Department of Neurosurgery of the 'Ramón y Cajal' Special Centre in Madrid, a series of 100 patients with head injuries treated with citicoline until discharge were studied, and their results were compared to those of another series of

Figure 14. Concentrations of radioactivity in the liver (a), brain (b) and kidneys (c) of rats at different time points after injecting double-labelled citicoline at a dose of 2 mg/kg. All values represent the means obtained from 10 animals.



100 patients with similar characteristics but who did not receive citicoline [344]. Treatment with citicoline was started at doses of 600-1,200 mg/d intraperitoneally and switched to 300-900 mg/d orally in the rehabilitation phase. The course was monitored by assessing the mean coma duration, the persistence of neurological and psychic symptoms, the WAIS test, and electrophysiological studies of muscle tension. The results suggested that the addition of citicoline to the treatment regimen caused a decrease in the duration of posttraumatic coma and the rate of both neurological and psychic sequelae and achieved a better response in recovery from intellectual disorders and motor deficits.

In a national survey conducted in France, Ragueneau et al [345] recorded 921 cases of severe head injury, i.e., those with an initial score on the Glasgow Coma Scale (GCS) of 8 or less. Of these, 219 patients had been treated with citicoline, which allowed for their distribution into two groups to compare the results obtained. No significant differences were found in mortality, but differences were seen in the number of dependent states, and the greatest effect was found in patients with an initial GCS score of 6-7 (Figure 18). Citicoline improved the quality of survival, allowing for more frequent social and familiar reinsertion, as well as a return to work or school. Mortality in head injuries essentially depends on the initial lesions, which, with the exception of epidural haematoma, are beyond any real therapeutic resolution.

Calatayud et al [346] reported the results of the influence of citicoline administration in the treatment of head injury. A total of 216 patients with initial GCS scores ranging from 5 to 10 were reported. Of these, 115 patients received treatment with citicoline. The mean citicoline dose administered was 4 g/d. The results showed that citicoline treatment decreased hospital stays ($p < 0.05$) and the duration of outpatient follow-up ($p < 0.001$), with the differences that were more marked in the group of patients with initial GCS scores ranging from 5 to 7), promoted the recovery of memory, motor disorders, higher neurological functions, and mood changes and improved global functional outcome (Table V).

Lozano [347] reported the impact of citicoline therapy on the course of posttraumatic cerebral oedema in a study conducted in 78 cases of head injury with initial GCS scores ranging from 5 to 7. In all cases, a computerised tomograph of the head was collected at the start and end of the study to assess changes in the tomographic image of cere-

bral oedema. Other parameters investigated included the duration of hospital stay and the extent of autonomy at hospital discharge. Citicoline was administered to 39 patients for the first 2 weeks at doses ranging from 3 to 6 g/d by intravenous infusion. After 14 days of citicoline treatment, the images of cerebral oedema evolved as shown in Figure 19. Cerebral oedema had been reduced or normalised in a higher number of patients treated with citicoline compared to control patients, with the differences being highly significant ($p < 0.005$). No significant differences were observed between groups in the therapeutic requirements or treatments received. The mean hospital stay was 28.718 ± 21.6 days for the group receiving active treatment and 37.323 ± 35.22 days for the control group, which was a statistically significant difference ($p < 0.001$). Differences in the final outcomes, assessed according to the GOS, did not reach statistical significance due to the small number of cases and special characteristics of this type of patient. However, a trend was seen toward a more favourable resolution in the group of patients that were treated with citicoline (Table VI).

Levin [348] conducted a study in 14 patients with postconcussional syndrome following a mild to moderate head injury. This syndrome is characterised by symptoms such as headache, dizziness, mnesic disorders and sleep disturbances. In this study, patients treated with citicoline for one month experienced improvements in memory tests, particularly recognition tests, that were statistically significant compared to a placebo. Figure 20 shows the changes in symptoms after one month of treatment. Greater improvements were achieved in patients that were treated with citicoline compared to placebo patients, with the exception of gastrointestinal discomfort. Dizziness was significantly more common in patients from the placebo group after one month of study. However, in a simple-blind study in patients with mild head injuries [349], the authors were unable to demonstrate differences between citicoline and control with regard to the evolution of postconcussional symptoms.

León-Carrión et al [350-352] investigated the effects of citicoline on posttraumatic memory disorders in a series of studies. In a group of 7 patients with severe memory deficits, these authors investigated the effects of administering 1 g citicoline on cerebral blood flow (CBF), as measured by the ^{133}Xe inhalation technique. Two measurements were made, one at baseline and the other at 48 hours, under the same conditions, except that patients had taken the drug one hour before the test. All patients showed a significant hypoperfusion in the inferoposterior area of the left femo-

Figure 15. Evolution of ^{14}C-phospholipid concentrations in rat brains after intravenous administration of double-labelled citicoline. The concentrations represent the means of three animals and are expressed as a percentage of the total radioactivity corresponding to ^{14}C in the brain.

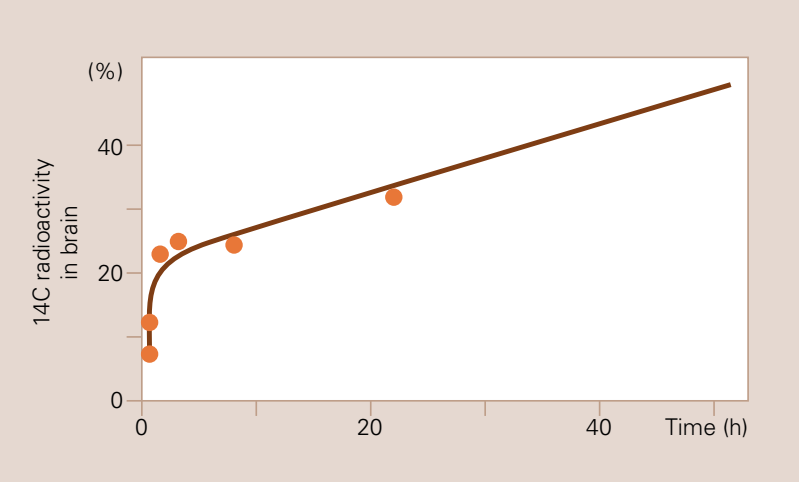


Figure 16. Total excretion of radioactivity (percentage of total administered) for 5 days after oral administration of ^{14}C -Citicoline. The mean values of six individuals are shown.

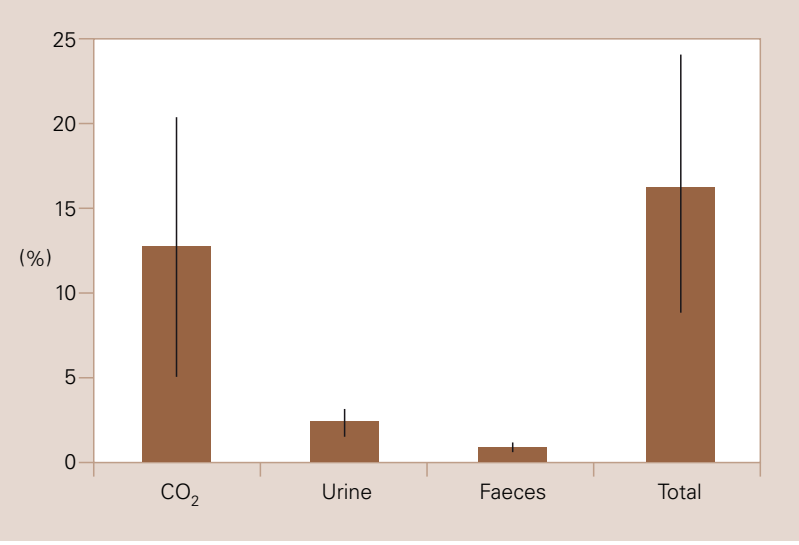


Figure 17. Normalisation of the state of consciousness in relation to time and treatment; $p < 0.01$ at day 60.

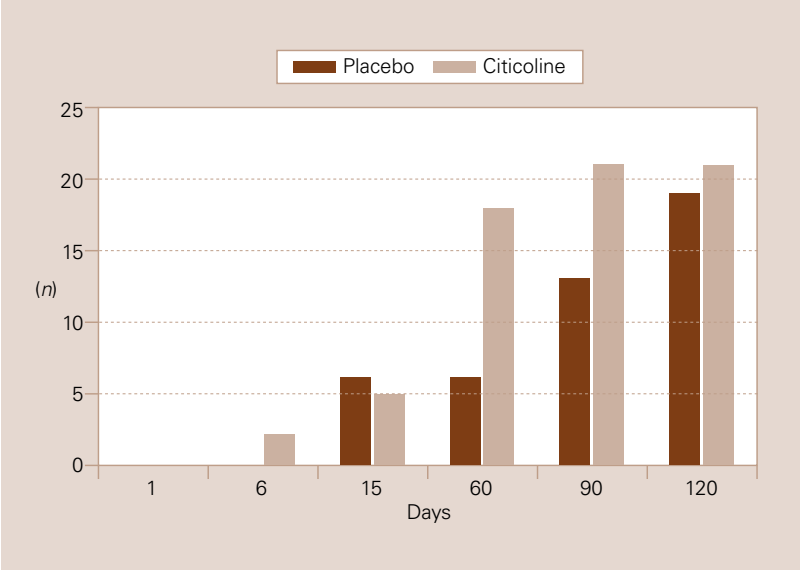


Table IV. Final results according to treatment.

	Glasgow Outcome Scale				
	I	II	III	IV	V
Placebo group	12	5	4	3	6
Citicoline group	11	9	3	2	5

ral lobe in the first measurement that disappeared following citicoline administration. In a second study, 10 patients with severe memory deficits were randomised into two groups. Both patient groups were subjected to a short memory rehabilitation program. One group received 1 g/d p.o. citicoline for the 3 months that the neuropsychological treatment program lasted, whereas the other group was given a placebo. The results obtained are shown in Table VII. Neuropsychological rehabilitation associated with citicoline resulted in improvements in all evaluated areas and reached statistical significance in verbal fluency and the word recall Luria test.

As a final conclusion, it has been widely shown that patients who have sustained a head injury, particularly those with an initial GCS score of 5-7, benefit from the addition of citicoline into their therapeutic regimen because this drug accelerates cerebral oedema reabsorption and recovery of both consciousness and neurological disorders, resulting in a shorter hospital stay and improved quality of survival [353]. Moreover, in cases of mild to moderate head injury, citicoline significantly decreases the duration and severity of the so-called postconcussional syndrome and improves memory deficits. A Cochrane review of citicoline for the treatment of head injury will soon be available [354]. In addition, there is a new, ongoing clinical trial in the United States, the COBRIT trial, to evaluate the effects of citicoline in patients with head injuries [355].

Acute cerebrovascular disease and sequelae

The neurobiological processes involved in the pathophysiology of cerebral ischaemia are extremely complex [356]. For this reason, some authors postulate that multifunctional treatments [357-362] are needed for this disease. As has been shown experimentally, citicoline is a drug that has pleiotropic actions, including the activation of neuronal metabolism, stabilisation of neuronal membranes and their function and normalisation of neurotransmission [15,34-36,148,221,222]. Various studies with citicoline that were conducted in the 1960s suggested its efficacy to reduce neurological symptoms in patients with cerebral ischaemia [363,364].

Hazama et al [365] conducted a double-blind study to assess the effect of citicoline on functional recovery from hemiplegia in 165 patients with cerebrovascular disease. These authors showed that citicoline, at a dose of 1,000 mg/d for 8 weeks, was superior to a placebo, particularly for motor recovery in the lower limbs, and concluded that citicoline promotes natural recovery from hemiplegia.

Goas et al [366] conducted a double-blind study comparing citicoline (750 mg/d/10 d i.v.) to placebo in 64 patients with cerebral infarction starting less than 48 hours prior to the stroke onset. The assessments at 3 months showed citicoline to be superior to placebo for improving motor deficit ($p < 0.05$), hypertonia ($p < 0.03$), gait recovery ($p < 0.02$), changes over time in electroencephalographic tracings ($p < 0.01$) and psychometric tests ($p < 0.05$), achieving a higher number of independent states (51.6% with citicoline; 24.24% with placebo) (Fig-

ure 21). In a study with the same characteristics, Boudouresques et al [367] achieved similar results. This study included 52 patients, 27 of whom received citicoline (750 mg/d/10 d i.v.), and 25 of whom received a placebo. An assessment was made at 10 days, and the assessment showed that citicoline-treated patients had a better course with regard to consciousness disorders. Recovery of consciousness occurred in 66.7% of the citicoline cases compared to 32.0% of the placebo group ($p < 0.01$), and deficit syndromes (82.6% and 54.5% of patients recovered with citicoline and placebo, respectively; $p < 0.04$) and electroencephalographic tracings (83.3% with citicoline vs. 35.3% with placebo; $p < 0.01$) were improved in the citicoline group. In both studies, citicoline tolerability was rated as excellent by investigators.

In a double-blind study of citicoline (1 g/d/30 d i.v.) vs. placebo in a sample of 33 patients, Corso et al [368] noted that at the end of the study, the deficit syndrome after acute stroke had improved in 76.5% of the patients treated with citicoline ($p < 0.01$ vs. placebo), and improved electroencephalographic tracings were seen in 70.6% of patients ($p < 0.01$ vs. placebo).

Tazaki et al [369] performed a double-blind, prospective, multicenter, placebo-controlled study on the value of citicoline for the treatment of acute cerebral infarction. Sixty-three Japanese academic centres participated in this study, in which a total of 272 patients were enrolled, following strict inclusion criteria. Patients were randomised to receive 1 g/d i.v. of citicoline or saline (placebo) for 14 days. At the end of the treatment, citicoline was shown to significantly improve consciousness (51% *vs.* 33% for placebo; $p < 0.05$), as well as overall improvement (52% vs. 26%; $p < 0.01$) and overall usefulness rates (47% vs. 24%; $p < 0.001$). In addition, fewer complications occurred in the citicoline-treated patient group (1%) compared to the placebo group (8.1%). These authors concluded that citicoline is an effective and safe drug for the treatment of acute cerebral infarction. These results agree with those reported by others [370-373].

Guillén et al [374] reported a comparative, randomised study on the efficacy of citicoline for treating acute ischaemic stroke compared to conventional therapy and showed a significantly higher improvement in the citicoline group compared to the control group. In open-label studies by Bruhwyler et al [375] and Fridman et al [376], better results favouring citicoline were also achieved, with significant clinical improvements in patients and an excellent safety profile of the drug. Álvarez and González [377] reported the beneficial effects of citicoline in a double-blind study conducted in Venezuela. León-Jiménez et al [378] evaluated the correlation between citicoline exposure and functional outcome at discharge and at 30 and 90 days post-stroke in a retrospective, case-controlled design on systematic descriptive databases from three referral hospitals in Mexico. Clinical records of 173 consecutively registered patients were analysed, 86 of whom were treated with citicoline within the

Figure 18. Effect of treatment with citicoline on final results. Results are expressed as percentages. [a] $p < 0.001$ vs. patients not treated with citicoline.

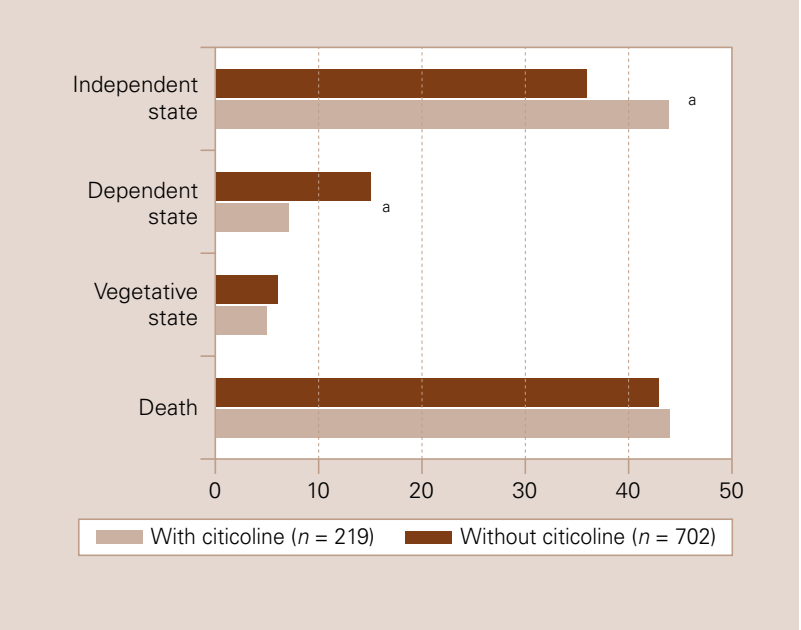


Table V. Final result, evaluated with the Glasgow Outcome Scale (GOS), in relation to treatment ($p < 0.05$).

	Citicoline	Control
GOS I	77	51
GOS II	19	31
GOS III	1	7
GOS IV	0	2
GOS V	18	10

Figure 19. Evolution of the tomographic image of cerebral oedema after 14 days of treatment ($p < 0.005$).

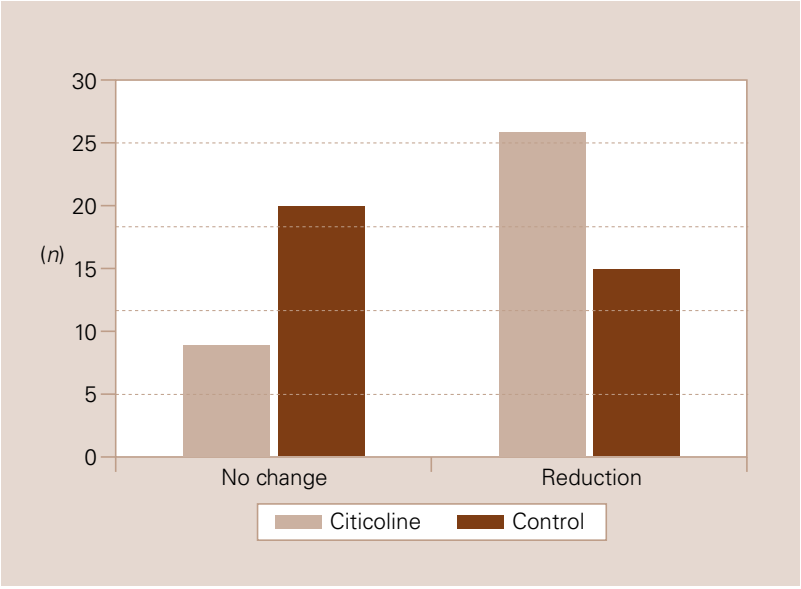


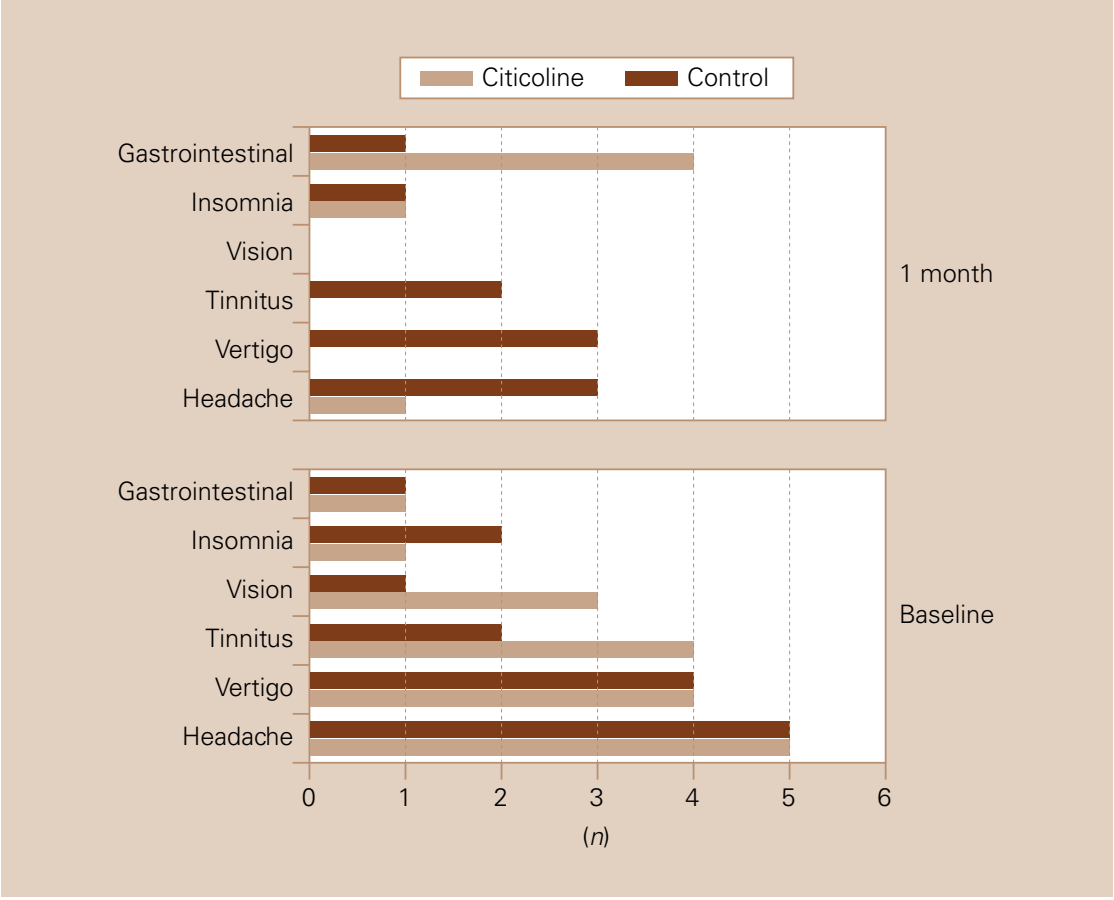
Table VI. Final result, evaluated with the Glasgow Outcome Scale (GOS), in relation to treatment (n.s.).

	Citicoline	Control
GOS I	15	11
GOS II	8	8
GOS III	6	7
GOS IV	4	6
GOS V	6	7

first 48 h after acute ischaemic stroke. The remaining 87 were untreated, randomly selected controls matched for age (± 5 years), gender and NIHSS (± 1 point) at hospital admission. Pretreatment conditions were similar between groups. Compared with controls, exposure to citicoline was associated with a significantly lower 30-day mean and median modified Rankin score (for both, $p < 0.05$). After paired multivariate analyses (controlled for NIHSS, age, gender, hospital arrival in < 24 h, thrombolysis and comorbidities) citicoline was independently associated with a lower 90-day mortality risk ($p = 0.047$) and fewer in-hospital complications (mainly infections and sepsis, $p = 0.001$). In this observational study, citicoline use was associated with a better functional status and lower rates of short-term mortality, possibly due to fewer in-hospital systemic complications.

In 1997, a study on oral citicoline for the treatment of acute ischaemic stroke was started in the United States. The first clinical trial was a randomised, dose-response study [379]. This double-blind, randomised, multicenter study compared 3 citicoline doses (500 mg, 1,000 mg and 2,000 mg, given orally) to a placebo to document drug safety, determine the optimum dose and collect data on the efficacy of citicoline for the treatment of acute ischaemic stroke. A total of 259 patients with ischaemic strokes in the territory of the middle cerebral artery were recruited within 24 hours of symptom onset. The patients were randomised into four groups: administration of placebo or 500, 1,000 or 2,000 mg/d of oral citicoline for 6 weeks. Patient recovery was assessed at the end of the 6-week treatment period and after a subsequent follow-up period of 6 weeks. The main efficacy endpoint was the Barthel Index (BI) at 12 weeks. Secondary endpoints included the modified Rankin Scale (mRS), the National Institutes of Health Stroke Scale (NIHSS), the Mini-Mental State Examination (MMSE), hospital stay duration and mortality. A significant difference favouring citicoline was found between groups in functional status (BI, mRS), neurological assessment (NIHSS) and cognitive function (MMSE). A significant effect of citicoline treatment was found at 12 weeks ($p < 0.05$) in a regression analysis of the BI, including the baseline NIHSS score as a covariate. The proportions of patients who achieved a BI score ranging from 85 to 100 were 39.1% for the placebo, 61.3% for the 500 mg dose, 39.4% for the 1,000 mg dose and 52.3% for the 2,000 mg dose. The odds ratios for an improved outcome were 2.0 for the 500 mg dose and 2.1 for the 2,000 mg dose. The lack of efficacy seen in the 1,000 mg group could have been due to the inclusion of patients into this group that were more overweight and had poorer neurological status at baseline. The mean score in the mRS was 3.1 with the placebo, 2.5 with 500 mg citicoline, 3.1 with 1,000 mg and 2.6 with 2,000 mg, and a significant difference was found between the 500 mg and placebo groups ($p < 0.03$). No citicoline-related serious adverse events or deaths were seen. According to these results, oral citicoline treatment achieves better functional out-

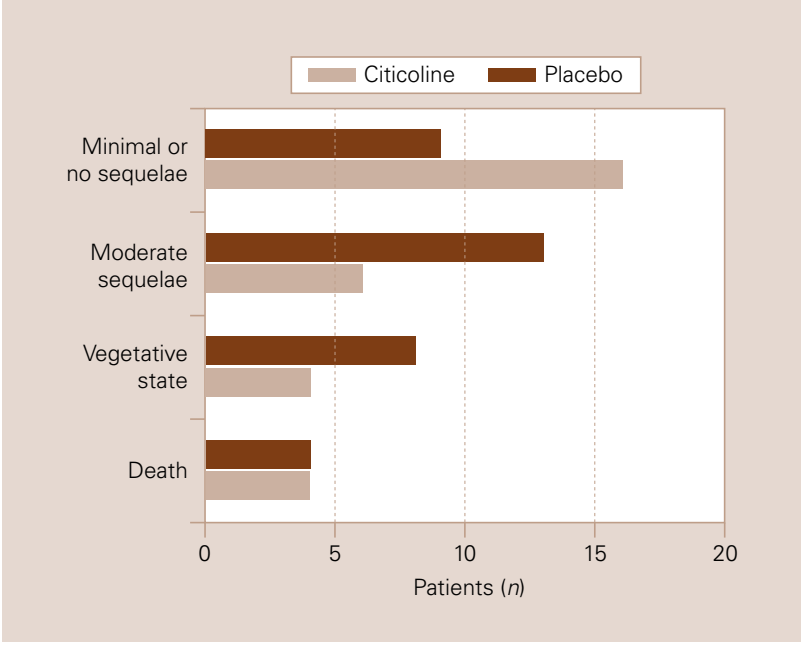
Figure 20. Evolution of post-concussional symptoms after one month of treatment with citicoline or placebo. The number of patients reporting each symptom is shown.



comes, and 500 mg is the most effective dose of citicoline.

A second multicenter, double-blind, placebo-controlled, randomised study [380] recruited 394 patients with acute ischaemic stroke arising in the middle cerebral artery less than 24 hours before and with a NIHSS score of 5 or higher. The patients were assigned oral administration of a placebo (n = 127) or 500 mg/d citicoline (n = 267). Treatment was continued for 6 weeks, and follow-up was subsequently conducted for 6 weeks. Mean entry time into the study was 12 hours after stroke onset, and the mean patient age was 71 years in the placebo group and 71 years in the citicoline group. Although the mean baseline NIHSS scores were similar in both groups, a greater proportion of patients in the citicoline group had a baseline NIHSS < 8 (34% vs. 22%; $p < 0.01$) in the placebo group. The planned primary endpoint (logistic regression for 5 BI categories) did not meet the proportional odd assumption and was therefore not reliable. No significant between-group differences were seen in any of the planned secondary variables, including a BI of 95 or higher at 12 weeks (placebo 40%, citicoline 40%) and the mortality rate (placebo 18%, citicoline 17%). However, a *post hoc* subgroup analysis showed that, in patients with moderate to severe stroke defined by a baseline NIHSS score of 8 or higher, treatment with citicoline conferred a greater chance of achieving complete recovery, defined as a BI = 95 at 12 weeks (21% placebo, 33% citicoline; $p = 0.05$), whereas no differences were found

Figure 21. Outcome in relation to treatment, highlighting the number of good results achieved with citicoline compared to the control group.



in patients with mild stroke (i.e., with a baseline NIHSS score < 8). No serious adverse events attributable to the drug were detected, which attests to its safety. Based on these data, citicoline may be considered a safe drug that may induce favourable effects in patients with moderate to severe acute ischaemic stroke.

The last clinical study conducted in the United States was the ECCO 2000 study [381]. This study had similar characteristics to the previous ones and enrolled 899 patients with moderate to severe acute ischaemic stroke (baseline NIHSS score = 8) arising in the middle cerebral artery within the past 24 hours. The patients were randomised to receive 2,000 mg/d citicoline (n = 453) or placebo (n = 446) orally for 6 weeks, with a subsequent follow-up for 6 weeks. The primary study endpoint was the proportion of patients that had a reduction in the NIHSS scale by 7 or more points at 12 weeks. At the end of the study, 51% of the patients in the placebo group and 52% of the patients in the citicoline group achieved reductions in the NIHSS scale of 7 or more points, with no significant between-group differences. In contrast, there was a trend favouring citicoline in the achievement of complete neurological recovery, as defined by a score of 1 or less on the NIHSS scale (40% with citicoline vs. 35% with placebo; p = 0.056), and in complete functional recovery, as defined by a BI score of 95 or higher (40% with citicoline *vs.* 35% with placebo; p = 0.108). With regard to the mRS, 20% of patients in the placebo group achieved complete recovery (mRS ≤ 1), as compared to 26% of patients in the citicoline group, a difference that is statistically significant (p = 0.025). There were no differences in mortality or incidence of serious adverse events between treatments, but a significant decrease was seen in the worsening of stroke (3% with citicoline vs. 6% with placebo; p = 0.02). However, the occurrence of a new stroke was decreased in patients treated with citicoline (2.9% with placebo vs. 1.8% with citicoline (i.e., 62.1% risk reduction). A *post hoc* analysis using the Generalized Estimating Equations (GEE) method defined by Tilley et al [382] assessed the effects of citicoline in a multiple outcome global assessment and considered the proportion of patients who had achieved complete recovery in all 3 scales used (i.e., achieved scores of 0-1 on the NIHSS, 0-1 on the mRS and ≥ 95 in the BI at 12 weeks). Citicoline was significantly superior to the placebo and achieved this complete recovery in 19% of the cases, compared to 14% in the placebo group (OR = 1.32; 95% CI = 1.03-1.69; p = 0.03).

The effects of citicoline on the reduction of cerebral infarct volume were investigated at the same time of other clinical study based on clinical outcomes. The first analysis was a pilot study to assess citicoline effects on lesion volume, as measured by diffusion-weighted magnetic resonance imaging (MRI) in patients with acute cerebral infarction [383]. This study recruited 12 patients from the first clinical study on citicoline in the United States [379]. Lesion growth was seen in 3 of the 4 patients treated with a placebo, whereas a decrease in lesion volume was noted in 7 of the 8 patients treated with citicoline (p < 0.01, with the baseline NIHSS as a covariate). A second, double-blind study designed for this purpose (i.e., to measure changes in lesion volume using diffusion-weighted techniques) recruited 100 patients who were randomised to receive 500 mg/d citicoline or placebo orally for 6 weeks [384]. These patients were enrolled within 24 hours of symptom onset and had a baseline NIHSS of 5 points or more and a lesion volume in the cerebral grey matter of 1-120 cm^3 in diffusion-weighted MRI. Neuroimaging techniques (diffusion-weighted MRI, T_2-weighted MRI, perfusion-weighted MRI and MRI angiography) were per-

Table VII. Scores (mean ± SD) obtained by patients before and after treatment.

	Group A (placebo + rehabilitation)		Group B (citicoline + rehabilitation)	
	Before	After	Before	After
Attention	95.60 ± 5.73	97.60 ± 2.19	82.00 ± 33.79	90.80 ± 20.57
Alertness	88.40 ± 8.65	96.80 ± 1.79	89.60 ± 17.74	98.80 ± 1.79
Verbal fluency	22.40 ± 9.91	23.60 ± 11.01	24.80 ± 14.65	31.80 ± 9.36 [a]
Benton test	8.20 ± 3.63	9.40 ± 6.95	8.80 ± 5.45	7.20 ± 3.70
Luria test	62.80 ± 13.24	62.00 ± 11.58	63.20 ± 17.31	71.00 ± 12.98 [a]

[a] $p < 0.05$ vs. before treatment.

formed at baseline and at weeks 1 and 12. The primary endpoint was progression of the ischaemic lesion from baseline to the final assessment at 12 weeks, as measured by MRI. The primary analysis planned could be performed in 41 patients treated with citicoline and 40 patients treated with placebo, and no significant differences were found. From baseline to 12 weeks, the ischaemic lesion volume expanded by 180 ± 107% in the placebo group and 34 ± 19% in the citicoline group. A secondary analysis showed that from week 1 to week 12, the lesion volume decreased by 6.9 ± 2.8 cm^3 in the placebo group and increased by 17.2 ± 2.6 cm^3 in the citicoline group ($p < 0.01$). The high correlation between the lesion volume reduction and clinical improvement, regardless of treatment, was a significant finding and supported the idea of using this methodology for assessing stroke treatments. In the ECCO 2000 study [381], a substudy was conducted to assess the effects of citicoline on lesion volume [385]. This substudy had three objectives. The first objective was to assess the effects of the drug on chronic lesion volume, as measured using MRI T_2 sequences in the entire patient sample, although this assessment could only be made in 676 patients. The second objective was to analyse the effects of citicoline on the change in lesion volume using diffusion-weighted MRI performed at baseline and at week 12. A total of 181 patients were recruited for this second objective, out of which 134 patients were evaluable. The third objective was methodological in nature, that is, an attempt was made to correlate clinical changes to volume changes and to determine whether lesion volume reduction was associated with clinical improvement. No significant differences were found in the assessment of chronic lesion volume (median of 25.0 cm^3 for citicoline and 31.3 cm^3 for placebo). The diffusion-weighted study showed that lesions increased 30.1 ± 20.5%, with a median of −8.7%, in the placebo group ($n = 71$), whereas the change in the citicoline group ($n = 63$) was 1.3 ± 14.3%, with a median of −22.9%, a non-significant difference ($p = 0.077$). However, the difference was significant ($p = 0.02$) when the logarithm of the change was analysed and the baseline NIHSS was introduced as a covariate. In this diffusion-weighted substudy, 54% of the patients in the placebo group and 67 % of the citicoline-treated patients were shown to have a decreased lesion volume compared to baseline, although the difference was not significant ($p = 0.122$). In patients with cortical lesions with volumes ranging from 1-120 cm^3 that were analysed at baseline, a lesion increase by 40.5 ± 28.7%, with a median of 4.5%, was seen in patients treated with placebo ($n = 47$), whereas in patients receiving treatment with citicoline ($n = 43$), the lesion increased by 7.3 ± 19.9%, with a median of –23.9%. The difference between groups was statistically significant ($p = 0.006$, median comparison). In the patient subgroup with initial cortical lesions with volumes of 1-120 cm^3, a decrease in lesion volume occurred in 47% of the patients in the placebo group and in 70% of the patients in the citicoline group. This difference was significant, with a p-value of 0.028. The decrease in volume was also significantly correlated with clinical improvements in patients.

Although the results obtained in studies conducted in the United States with oral citicoline for

the treatment of acute ischaemic stroke were inconclusive regarding citicoline efficacy or safety improving the outcome of the patients, there was a trend toward improved prognosis of treated patients. Because there was no neuroprotective drug that had been shown to be effective in the treatment of this severe condition [386] at that time, a meta-analysis was conducted of the results obtained with oral citicoline in the treatment of acute ischaemic stroke to examine the effects of the drug on neurological and functional recovery in patients [387]. Following the methods of the Cochrane Library [388] and the guidelines of the International Conference on Harmonization [389], a comprehensive literature search was performed in both Medline and our own literature database. This search found that only four double-blind, randomised clinical studies had been conducted with oral citicoline for the treatment of acute ischaemic stroke, namely, the four trials that were performed in the United States [379-381,384]. The total sample comprised 1652 patients, 686 patients in the placebo group and 966 patients in the citicoline group (381 with 500 mg/d, 66 with 1,000 mg/d and 519 with 2,000 mg/d). The first analysis was performed in the total patient sample, regardless of dose. With regard to complete neurological recovery (NIHSS ≤ 1) at 3 months, the odds ratio was 1.22 (95% CI = 0.98-1.52), which did not reach statistical significance (p = 0.07). In contrast, significant differences favouring citicoline were obtained in the analysis of patients who achieved virtually complete recovery in activities of daily living (BI ≥ 95) at 3 months (OR = 1.26; 95% CI = 1.02-1.55; p = 0.01) and functional recovery at 3 months, defined as a score of 1 or less in the mRS (OR = 1.36; 95% CI = 1.06-1.74; p = 0.01). Because the experience gathered in the above clinical studies suggested that the drug is more effective in patients with moderate to severe acute ischaemic stroke (baseline NIHSS ≥ 8), databases from the original studies were obtained, and patients who met this criterion and had optimum functional status prior to the stroke (mRS ≤ 1) were selected. Out of the entire sample, 1372 patients met these criteria and underwent the same assessment. In this case, the meta-analysis found statistically significant differences for all variables analysed (Table VIII).

To continue the analysis of these data, a pooling data analysis was performed [390] using individual data from each patient. This additional analysis included a sample of 1372 patients who met the established criteria of severity (baseline NIHSS ≥ 8), prior functional status (mRS ≤ 1), a therapeutic window not longer than 24 hours and consistent neuroimaging. The efficacy endpoint selected was total recovery at 3 months in the three scales analysed (mRS ≤ 1 + NIHSS ≤ 1 + BI ≥ 95), using the previously described GEE analysis [382]. Among these 1372 patients, 583 received a placebo and 789 received citicoline (264 patients received 500 mg, 40 patients received 1,000 mg and 485 patients received 2,000 mg). Total recovery at 3 months was achieved in 25.2% of the patients treated with citicoline and 20.2% of the patients in the placebo group (OR = 1.33; 95% CI = 1.10-1.62; p = 0.003), and the most effective dose was 2,000 mg. This dose resulted in complete recovery at 3 months in 27.9% of the patients who received the drug (OR = 1.38; 95% CI = 1.10-1.72; p = 0.004) (Figure 22). In addition, citicoline safety was similar to that of the placebo.

The preliminary results of a Cochrane review on the effects of choline precursors, including citicoline, in the treatment of acute and subacute stroke were reported in 2002 [391]. This meta-analysis collected data from 8 double-blind studies conducted with citicoline at doses ranging from 500 to 2,000 mg daily, administered both orally and intravenously. Despite study heterogeneity, citicoline treatment was associated with decreases in late mortality and disability rates: citicoline 611/1119 (64.6%) vs. placebo 561/844 (54.4%) (OR = 0.64; 95% CI = 0.53-0.77; p < 0.00001). To decrease the heterogeneity, the analysis was restricted to the 4 studies with large sample sizes (n > 100), and the positive effect persisted: citicoline 574/1048 (54.58%) vs. placebo 500/773 (64.7%) (OR = 0.70; 95% CI = 0.58-0.85; p < 0.0003). In the safety analysis, no differences were found in the mortality rate between citicoline and the placebo. The authors concluded that the formal meta-analysis of citicoline studies in acute and subacute stroke suggests a beneficial and substantial effect of the drug, with absolute reductions by 10-12% in the long-term disability and mortality rate (i.e., the number of patients with scores of 3 or higher in the modified Rankin scale was significantly decreased). These results agree with those previously reported for the pooled data analysis [390].

A pooled data analysis that evaluated the effect of citicoline on the increase in cerebral infarct size is also available [392]. Data used in this analysis came from two studies in which neuroimaging data had been obtained using MRI techniques [381,384]. The primary endpoint in this analysis was the percent change in infarct size from the start of the study to the end of the study, 3 months later. Data

were available for 111 patients receiving a placebo, 41 patients treated with citicoline 500 mg/d/6 weeks and 62 patients treated with citicoline 2,000 mg/d/6 weeks. Patients receiving the placebo experienced a mean increase of 84.7 ± 41.2%, and a dose-dependent effect was associated with citicoline: a mean increase of 34.0 ± 18.5% was observed with 500 mg citicoline, and an increase of 1.8 ± 14.5% was observed with 2,000 mg citicoline.

The benefits shown in these systematic reviews were also associated with reductions in the costs of integral treatment of patients with acute ischaemic stroke [393], with an average cost savings of €101.2-126.4 per patient treated. In patients with acute ischaemic stroke, treatment with placebo was more expensive and less effective in the scenarios of inpatient care and inpatient plus outpatient care after hospital discharge.

Sobrino et al [394] investigated whether administration of citicoline, started in the acute phase of stroke, could increase the endothelial progenitor cell (EPC) concentration in patients with ischaemic stroke. Forty-eight patients with first-ever non-lacunar ischaemic strokes were prospectively included in the study within 12 hours of symptom onset. Patients received treatment (n = 26) with oral citicoline (2,000 mg/day/6 week or no treatment (n = 22). EPC colonies were quantified as early outgrowth colonies forming a unit-endothelial cell (CFU-EC) at admission (previous to citicoline treatment) and day 7. The EPC increment during the first week was defined as the difference in the number of CFU-EC between day 7 and admission. The CFU-EC were similar at baseline between patients treated with citicoline and non-treated (7.7 ± 6.1 vs. 9.1 ± 7.3 CFU-EC; p = 0.819). However, patients treated with citicoline and recombinant tissue-plasminogen activator (rt-PA) had a higher EPC increment than patients treated with citicoline only or those who were not treated (35.4 ± 15.9 vs. 8.4 ± 8.1 vs. 0.9 ± 10.2 CFU-EC; p < 0.0001). In a logistic model, citicoline treatment (OR = 17.6; 95% CI = 2.3-137.5; p = 0.006) and co-treatment with citicoline and rt-PA (OR = 108.5; 95% CI = 2.9-1094.2; p = 0.001) were independently associated with an EPC increment ≥ 4 CFU-EC. The authors concluded that citicoline administration and citicoline and rt-PA co-administration increase the EPC concentration in acute ischaemic stroke. However, the molecular mechanism by which citicoline increases the concentration of EPCs remains to be clarified.

Regarding safety, a drug surveillance study involving 4191 acute stroke patients treated with citicoline was conducted in South Korea [395]. The aim of this study was to determine the efficacy and safety of oral citicoline in Korean patients with acute ischaemic stroke. Oral citicoline (500-4,000 mg/day) was administered within 24 h after acute ischaemic stroke in 3,736 patients (early group) and later than 24 h after acute ischaemic stroke in 455 patients (late group), and the treatments continued for at least 6 weeks. For the efficacy assessment, the primary outcomes were the patients' scores obtained with a short form of the National Institutes

Figure 22. Estimated probabilities (GEE analysis) of overall recovery three months after onset of symptoms. Overall recovery is defined as a consistent and persuasive difference in the proportion of patients who achieve scores of NIHSS ≤ 1, BI ≥ 95 and mRS ≤ 1 at the same time.

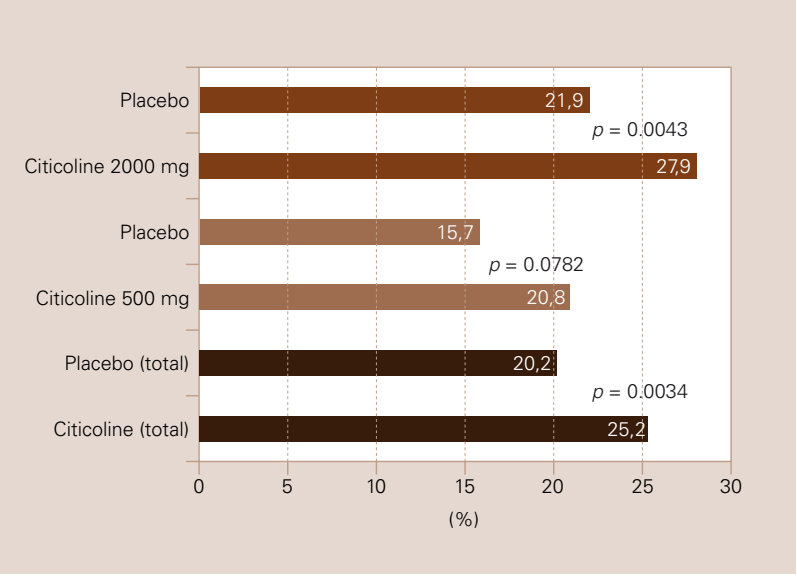


Table VIII. Results obtained after three months on individual scales.

	Studies (n)	Patients (n)	Peto odds ratio (95% CI)	p
NIHSS ≤ 1	4	1,372	1.34 (1.05-1.71)	0.020
mRS ≤ 1	4	1,351	1.45 (1.11-1.90)	0.007
BI ≥ 95	4	1,372	1.28 (1.03-1.59)	0.003

95% CI: 95% confidence interval; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; BI: Barthel index.

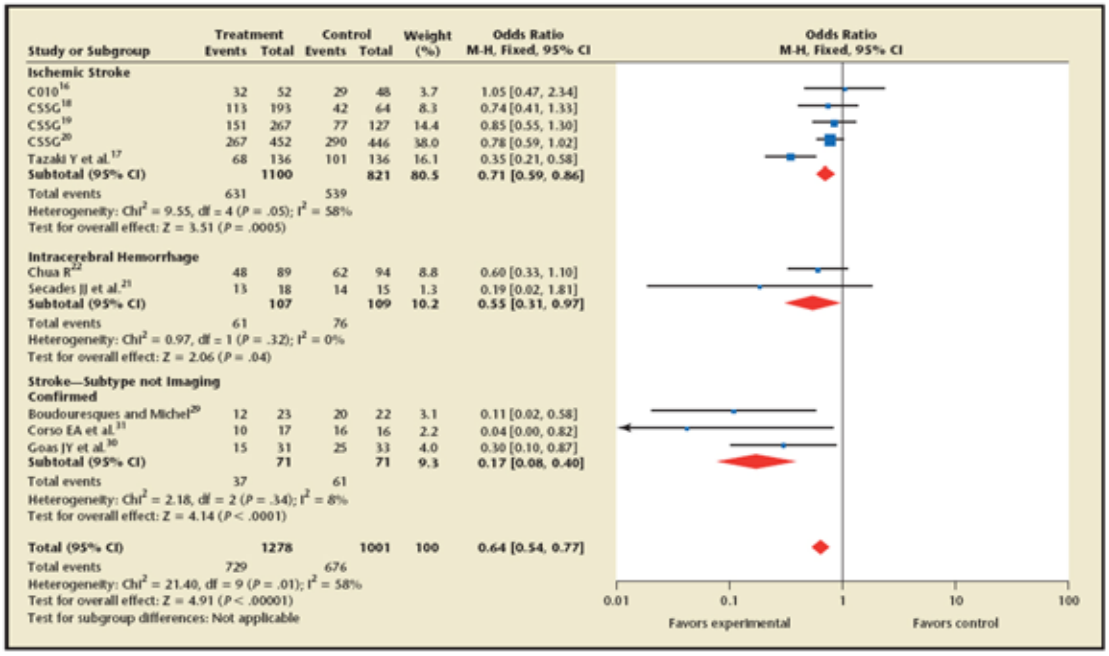
of Health Stroke Scale (s-NIHSS), a short form of the Barthel Index of activities of daily living (s-BI) and a modified Rankin Scale (mRS) at enrolment, after 6 weeks and at the end of therapy for those patients with extended treatment. All adverse reactions were monitored during the study period for safety assessment. All measured outcomes, including the s-NIHSS, s-BI and mRS, were improved after 6 weeks of therapy ($p < 0.05$). Further improvements were observed in 125 patients who continued citicoline therapy for more than 12 weeks compared with those who ended therapy at week 6. Improvements were more significant in the higher dose group (≥ 2,000 mg/day) ($p < 0.001$). The s-BI scores showed no differences between the early and late groups at the end of therapy. Citicoline safety was excellent; 37 side effects were observed in 31 patients (0.73%). The most frequent side effects were nervous system-related symptoms (8 of 37, 21.62%), followed by gastrointestinal symptoms (5 of 37, 13.5%). Oral citicoline improved neurological, functional and global outcomes in patients with acute ischaemic stroke without significant safety concerns.

A pilot study has been published on the safety and efficacy of citicoline for the treatment of primary intracerebral haemorrhage [396]. This study recruited 38 patients, aged 40 to 85 years, who were previously independent and were enrolled within 6 hours of symptom onset caused by primary intracerebral haemorrhage, as diagnosed by neuroimaging tests (CT or MRI). Patients had a baseline severity categorised by a score higher than 8 in the Glasgow Coma Scale and a score higher than 7 in the NIH stroke scale. The patients were randomised to 1 g/12 h of citicoline or placebo i.v. or orally for 2 weeks. The primary study objective was to assess treatment safety based on the occurrence of adverse events. The efficacy endpoint selected was the proportion of patients who had scores of 0-2 on the modified Rankin scale at 3 months. Nineteen patients were included in each group, and the groups were perfectly matched with regard to baseline characteristics. The adverse event rate did not differ between groups (4 cases each). With respect to efficacy, one patient from the placebo group was rated as independent (mRS < 3), compared to 5 patients from the citicoline group (OR = 5.38; 95% CI = 0.55-52; ns). In conclusion, citicoline appears to be a safe drug for patients with primary intracerebral haemorrhage, which may allow citicoline to be given to patients with clinical signs suggestive of stroke before neuroimaging tests are performed and at an earlier time than usual. With respect to efficacy, very promising data for a favourable outcome have been obtained, but they should be confirmed in a larger study. Recently, Eribal et al [397] communicated the results of the RICH trial performed in the Philippines. This study was conceived to investigate the role of neuroprotectants, particularly citicoline, in intracerebral supratentorial haemorrhage, which, to date, has a paucity of data on proven effective therapies. This trial was a randomised, double-blind, placebo-controlled, multicentre, parallel group study on patients with first-time supratentorial intracerebral haemorrhages. The patients were given either 4 g citicoline or a placebo for 14 days from the index stroke. A total of 182 patients were enrolled in the study. The mean age was similar for both groups (56.90 ± 11.45 for citicoline and 57.61 ± 11.83 for placebo). The comorbidities were similar, except for the significantly higher number of diabetic patients in the citicoline group. The results showed that there were more patients with favourable Barthel Index scores (2.2% vs. 0%, 9.2% vs. 8.5% and 50.8% vs. 31.9%) in the citicoline group than in the placebo group, respectively. However, the difference was only clinically significant after day 90. Patients had more favourable mRS scores (7.9% vs. 13.4%, 18.2% vs. 20.3% and 46.1% vs. 33.8%) in the citicoline group than in the placebo group; however, this difference occurred only on day 90 and was not statistically significant. The NIHSS did not differ between groups, with scores of 76.3% vs. 75.6%, 93.9% vs. 91.9% and 96.8% vs. 94.3%, respectively. Mortality was slightly higher in the citicoline group (11 patients) than in the placebo group (10 patients), but this difference was not statistically significant. The incidence of adverse events in both groups was not significantly different. For these authors, citicoline was effective in improving BI and mRS scores on the attainment of functional independence beginning on day 90 post-stroke compared to the placebo. Iranmanesh and Vakilian demonstrated the efficiency of citicoline in increasing the muscular strength of patients with nontraumatic cerebral haemorrhages in a double-blind, randomised clinical trial [398]. Thus, citicoline could play a role in the pharmacological treatment of patients with intracerebral haemorrhages [399].

In a new meta-analysis study that included all double-blind studies performed with citicoline in acute stroke patients, Saver [400] suggested that citicoline has beneficial effects on long-term death and disability rates in this type of patient (Figure 23).

Ortega et al [401] planned a study with the goal of assessing the efficacy and safety of a citicoline

Figure 23. Death or dependency at long-term follow-up. Forest plot meta-analysis of the effect of citicoline vs. control in trials enrolling patients with ischaemic stroke, intracerebral haemorrhage and stroke without imaging confirmation of subtype. C010: citicoline 010 trial; CI: confidence interval; CSSG: Citicoline Stroke Study Group; df: degree of freedom; Fixed: fixed-effects model; M-H: Mantel-Haenszel estimate. Reprinted with permission from J.L. Saver. *Citicoline: update on a promising and widely available agent for neuroprotection and neurorepair*. Rev Neurol Dis 2008; 5: 167-77.



treatment from the first stroke event until the sixth month to preserve neurocognitive functions. They included 347 patients with first stroke events. Cognitive functions were evaluated by a complete neuropsychological battery six weeks (± 3 days) and six months (± 7 days) after the strokes. All subjects received citicoline treatment (2 g/d) until the sixth week. Randomly, approximately half of the sample continued the citicoline treatment (1 g/d) until the sixth month. Those patients who were not treated with citicoline showed statistically significant higher cognitive impairment in attention and executive functions (OR = 1.725; 95% CI = 1.090-2.729; p = 0.019) and temporal orientation (OR = 1.728; 95% CI = 1.021-2.927; p = 0.042). The authors concluded that citicoline treatment until the sixth month in patients with first ischaemic stroke events is safe and efficient in improving neurocognitive functions.

In conclusion, it has been adequately shown that patients with acute stroke and sequelae may benefit from citicoline treatment by achieving better functional and neurological recovery and that this is a safe and well-tolerated treatment, as recognised by various studies [402-411] and some agencies [412-413]. There is also a new, ongoing trial in Europe, the ICTUS trial [414-416], to corroborate the data obtained with citicoline.

Cognitive disorders

Various investigations in recent years on brain ageing have led to the increased importance of changes in neuronal metabolism as a factor that is involved in the pathophysiology of this process. In the senile brain, there is a general decrease in enzyme activities related to energy metabolism and more specific biochemical changes affecting lipid and nucleic acid metabolism. It has also been shown that specific changes in certain neurotransmitters (dopamine, acetylcholine) and hormones (growth hormone, prolactin) are associated in both ageing processes and certain presenile and senile diseases [417].

Table IX. Percentage remission and symptomatic improvement ($p < 0.001$ for each symptom in relation to the onset of treatment).

	Patients (*n*)	Remission (%)	Improvement (%)
State of mood	1521	38.2%	40.9%
Emotivity	1559	36.9%	39.7%
Restlessness	1504	41.3%	34.1%
Own initiative	1378	35.8%	32.9%
Short-term memory	1614	26.0%	45.5%
Interest in the environment	1410	38.3%	34.5%
Appearance	1132	40.0%	26.9%
Vertigo	1463	59.4%	31.3%
Mobility	1234	35.2%	30.5%
Headache	1425	57.7%	31.2%

As shown in the aforementioned experimental studies, citicoline increases phospholipid synthesis and glucose uptake in the brain in conditions in which these activities are decreased. Citicoline also influences the metabolism of neurotransmitters and increases dopamine synthesis in certain brain regions. Based on these facts, many clinical trials have been conducted to assess the efficacy of citicoline in the treatment of cognitive disorders associated with brain ageing, chronic cerebral vascular disease and dementia [418]. Using magnetic resonance spectroscopy techniques, citicoline has been shown to stimulate phosphatidylcholine synthesis in the brain [419-421] and improve the energetic cerebral metabolism of elderly subjects [422], which is related to improvements in their cognitive capacities [423], particularly memory [424-426] and reaction time [427]. In addition, an effect on preventing cognitive impairment after a first-ever ischaemic stroke has been described [401].

In one early study conducted in this field, Madariaga et al [428] showed that, in a group of female senile patients, citicoline treatment induced improvements in memory, cooperation and the capacity for a relationship with the environment. Fassio et al [429] discussed the value of citicoline in psychogeriatrics and stressed that the use of citicoline as background treatment allows the reduction of the dosages of psychoactive drugs that are routinely used in psychogeriatrics. Many studies have shown the value of citicoline for treating the senile cerebral involution, decreasing its characteristic symptoms [430-439]. In an open-label, controlled study conducted on a group of 30 patients with senile involutive brain disease, Lingetti et al [430] achieved symptomatic improvements in 83.3% of cases and emphasised the absence of treatment-related side effects. Stramba-Badiale and Scillieri [431] showed significant improvements in scores of the Fishback Mental Status Questionnaire in a group of 24 elderly subjects after 20 days of treatment with 500 mg/d i.m. citicoline. Bonavita et al [432] emphasised the efficacy of citicoline in promoting changes in certain neuropsychiatric symptoms, including memory and attention, in senile patients without causing side effects. Lozano et al [433] reviewed a series of 2067 elderly patients who were treated with citicoline at doses of 300-600 mg/d for 2 months. Table IX gives the results obtained based on the remission and improvement of certain neuropsychic symptoms. Palleschi and Capobianco [434] showed significant improvements in scores of the SCAG and Mini-Mental State Examination scales in patients with pathological brain ageing following citicoline treatment. In a multicentre study with 502 senile patients, Schergna and Lupo [435] showed that citicoline induced significant improvements in attention, behaviour, relational life and independence. No side effects occurred that were associated with this treatment. Suryani et al [436] showed that citicoline was effective in the treatment of memory deficits in the elderly, achieving significant and progressive improvements in all parameters analysed (Table X). Citicoline is able to improve the scores of senile patients in various scales, such as the Plutchik scale [437], Trail Making Test, Randt Memory Test and Toulouse-Piéron Attention Test [438,439].

The administration of citicoline to healthy adult individuals has shown that citicoline acts on the anterior pituitary gland, inducing increased growth hormone secretion and decreased prolactin secretion due to the activation of the dopaminergic system [440,441]. Ceda et al [442] showed that citicoline increases growth hormone secretion, both basal hormone secretion and hormone secretion that is stimulated by the growth hormone-releasing hormone, in elderly patients. This secretion is impaired in such individuals and is impaired to an even greater extent in patients with degenerative brain diseases.

One of the main causes of cognitive impairment in the elderly is chronic cerebral vascular disease,

Table X. Scores for the repetition of digits, an adaptation by Wechsler of the Stanford-Benet logical history test, the Bali image memorisation test and memory deficits and physical disorders reported by patients before and after treatment with citicoline. Values are expressed as means ± SD.

	Baseline (n = 10)	After treatment		
		1 week (n = 10)	2 weeks (n = 10)	3 weeks (n = 6)
Direct repetition of digits	14.6 ± 4.6	19.6 ± 5.6 [b]	20.2 ± 4.5 [b]	22.8 ± 6.0 [b]
Reverse repetition of digits	5.60 ± 4.1	7.30 ± 3.4 [b]	11.3 ± 7.1 [b]	12.1 ± 7.7 [b]
Logic history test	6.10 ± 4.4	9.60 ± 3.8 [b]	12.7 ± 3.7 [b]	13.6 ± 4.8 [b]
Bali images test	5.20 ± 3.2	9.30 ± 3.5 [b]	11.7 ± 3.4 [b]	12.0 ± 2.4 [b]
Memory deficits	2.5 ± 0.9	1.00 ± 0.9 [a]	0.30 ± 0.4 [b]	0.30 ± 0.5 [b]
Physical disorders	2.3 ± 0.9	1.00 ± 0.8 [a]	0.20 ± 0.6 [b]	0.10 ± 0.4 [b]

[a] $p < 0.05$; [b] $p < 0.01$, vs. baseline values.

also called cerebral insufficiency, whose maximum degree of clinical expression is vascular dementia. A multicentre, randomised, double-blind study of citicoline vs. placebo assessed the efficacy of citicoline for the treatment of patients with chronic vascular disease [443]. In this study, 33 patients received treatment with 1 g/d citicoline or saline via intravenous infusion for 28 days. At the end of the treatment period, significant improvements were noted in the citicoline-treated group in the Bender-Gestalt test, Hamilton scale for depression, Parkside scale, neurological assessment scale and attention test. Falchi Delitalia et al [444] and Moglia et al [445] noted that the observed clinical improvement was associated with improved EEG tracing in these patients. Merchan et al [446] showed gradual improvements in symptoms associated with cerebrovascular insufficiency in a group of 40 elderly patients treated with citicoline at a dose of 1 g/d i.m. for 60 days.

Agnoli et al [447] conducted a double-blind study in 100 patients with chronic cerebral vascular disease in whom the effectiveness of 1 g/d/28 d i.v. citicoline administration was assessed compared to a placebo. After the treatment period, the group of citicoline-treated patients showed statistically significant improvements in the scores obtained in the Hamilton scale for depression, in the modified Parkside behaviour rating scale and in psychometric and observational tests. It was concluded that citicoline improves perceptual-motor capacity and attention in these patients in addition to having a stabilising effect on behaviour. Sinforani et al [448], Motta et al [449] and Rossi and Zanardi [450] achieved similar results in their respective studies. The best clinical and behavioural results in neuropsycholigical tests were observed in patients with diffuse cerebral vascular disease [451-454].

Eberhardt and Derr [455] conducted a double-blind crossover study to assess the efficacy and tolerability of citicoline in patients with senile cerebral insufficiency. This study enrolled 111 patients with a mean age of 74.6 ± 6.9 years and a clinical diagnosis of senile cerebral insufficiency. After a placebo washout period, two homogeneous groups were formed, one of which received treatment with 600 mg/d p.o. citicoline for 5 weeks and placebo for 5 additional weeks, with a placebo washout period between both treatments. The reverse administration order was used in the other group. Controls were performed at 2, 7, 9 and 12 weeks. Citicoline significantly improved the clinical status in all six tests used (number recall, labyrinth, number connection, Neuropsychological Assessment Scale or NAS, Geriatric Observation Scale or NAB and SCAG) as initial treatment and provided a statistically significant additional improvement as a second treatment after placebo, which achieved some degree of improvement in 5 of the 6 tests. Between-subject comparisons also showed a superior efficacy of citicoline. Table XI shows the proportions of

Table XI. Percentage of patients who improved in each group in relation to treatment initiation with citicoline or placebo.

	Group I		Group II	
	Citicoline	Placebo	Placebo	Citicoline
Numerical counting	47	31	21	52
Labyrinth	73	69	71	83
Numerical connection	67	76	67	87
NAS	57	41	44	69
NAB	63	57	48	67
SCAG	80	73	65	83

NAS: Neuropsychological Self-Assessment Scale; NAB: Gerontopsychological Observation Scale; SCAG: Sandoz Clinical Assessment Geriatric Scale.

patients who improved in each treatment phase in both groups. No treatment-associated severe side effects were seen. The authors concluded that these results support the efficacy of citicoline for the treatment of senile cerebral insufficiency and demonstrate the excellent tolerability of the drug in geriatric patients. These benefits are due to the capacity of citicoline to inhibit phospholipid degradation in neuronal membranes, increase choline plasma levels and activate the synthesis of structural phospholipids and the synthesis and release of catecholamines. The effects of citicoline on test improvement were also shown to persist after switching to placebo, suggesting that they are related to the neuronal metabolic process that restores and maintains neuronal function.

Chandra [456] reported the results of a double-blind study on the treatment of multi-infarction dementia with citicoline. This study enrolled 146 patients who were randomised into two groups, one of which received treatment with 750 mg/d i.v. citicoline and the other receiving saline for 2 months, although the follow-up period was prolonged for up to 10 months. At the end of the treatment period, citicoline-treated patients showed significant improvements in MMSE scores. In contrast, these scores slightly worsened in the placebo group. After 10 months, citicoline-treated patients achieved sustained improvement, whereas patients in the placebo group continued to worsen.

Piccoli et al [457] reported the results of a double-blind study conducted in 92 patients with chronic cerebral vascular disease treated with citicoline (1,000 mg/d i.m.) or placebo in 2 treatment cycles of 4 weeks each, separated by a one-week interval. Forty-six patients were randomised to each group, and both groups were fully matched with regard to cognitive impairment. Psychometric assessments were performed using the Toulouse-Piéron test (attention to non-verbal stimuli), Randt memory test and SCAG scale (a measure of behaviour and emotional control). A between-group comparison revealed significant improvements in the citicoline group in the attention tests, with a decreased number of incorrect answers in the Toulouse-Piéron test ($p < 0.05$), in mnesic capacities according to the general information subtest of the Randt memory tests ($p < 0.05$) and in the affective disorder score on the SCAG scale ($p < 0.02$). In addition to being clinically effective, citicoline was shown to be a very safe drug, as no adverse effects associated with treatment were detected.

Capurso et al [458] assessed the efficacy of citicoline for treating chronic cerebrovascular disease in a multicentre, double-blind, placebo-controlled study. Cognitive and behavioural functions were assessed using psychometric scales and tests in 31 patients who were randomised to receive citicoline (17 cases) or placebo (16 cases). After a 2-week washout period, 3 treatment periods, each lasting 28 days, were started. Patients were given 1 g/d of citicoline or placebo via the intramuscular route. A 1-week washout period was left between each treatment cycle. Various cognitive functions improved in the group of citicoline-treated patients, particularly short-term and long-term memory. The Randt Memory Test showed constant improvements in several subtests, and cognitive and attention efficiency significantly improved. The GBS scale, which assesses behavioural indices, also showed improvements associated with citicoline treatment. The authors concluded that patients treated with citicoline showed significant improvements in cognitive functions, whereas placebo-treated patients showed no favourable trends. In addition, good tolerability of the drug was also reported.

Cohen et al [459] showed no beneficial effects of citicoline in their pilot study in patients with vascular dementia, according to current diagnostic criteria.

Using positron emission tomography, Tanaka et al [460] correlated cognitive improvement with a significant increase in cerebral blood flow in pa-

tients with vascular dementia who received citicoline treatment (1 g/d/1 week i.v.).

Lozano [461] reported the results of a study conducted by the Iberian-American Group for the study of Alzheimer's disease and Longevity (GIAL), aimed at assessing the status and course, after one year, of a group of patients with dementia-like psychic and organic impairment following diagnosis and classification of its cause as degenerative, vascular or mixed and treatment with oral citicoline. Citicoline 600 mg/d p.o. was administered for one year to 314 patients with a mean age of 75.02 ± 7.72 years to assess the course of their dementia during that time. The dementia was rated as degenerative in 41.1% of cases, whereas vascular dementia accounted for 39.5% of the cases and mixed dementia accounted for 11.4% of the cases. The MMSE and BI were used for assessment, and controls were performed at months 1, 3 and 12. MMSE scores significantly improved in vascular and mixed dementia and remained stable, with a trend toward improvement, in degenerative dementia. BI scores showed statistically significant improvements in each control and for each type of dementia. These results suggest that citicoline has a beneficial effect on the long-term course of dementia and is a safe treatment.

Corona et al [462] pointed out that the benefits of citicoline in the treatment of patients with dementia could be partly due to the ability of the drug to improve the activity of the noradrenergic, dopaminergic and serotonergic systems, as shown in a study assessing the changes over time in the CSF and urinary levels of metabolites from the monoamines involved in these systems during the treatment of patients with senile dementia of the Alzheimer type.

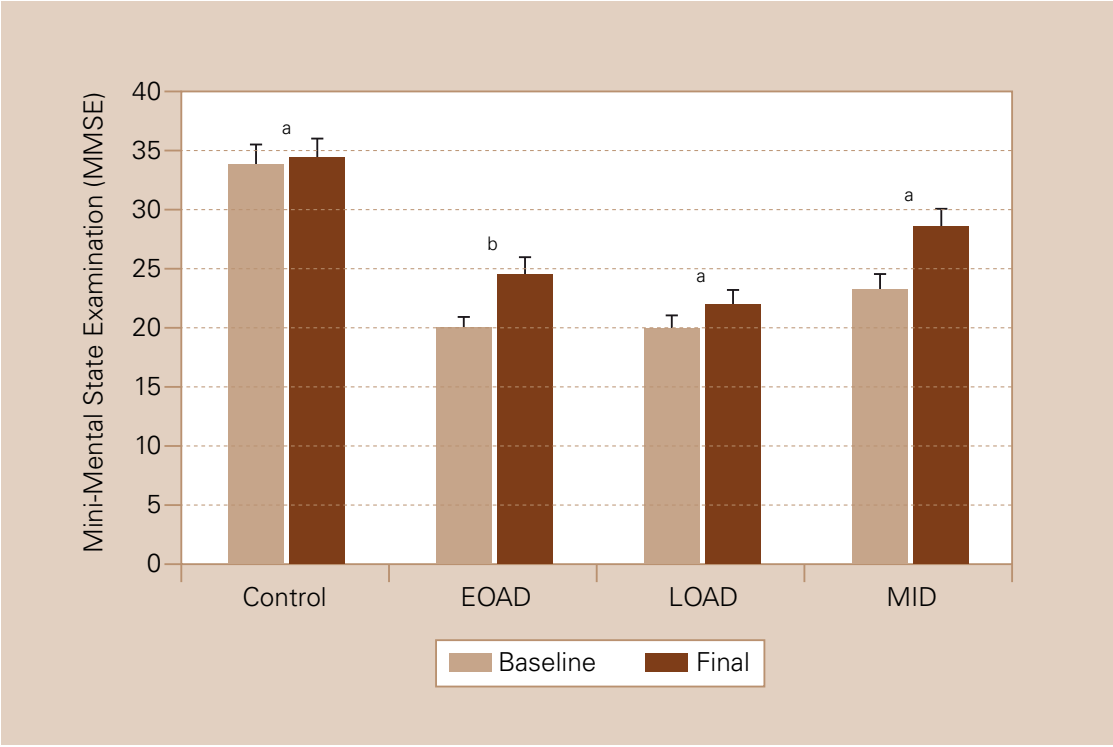
Cacabelos et al [463] conducted a study to assess the therapeutic effects of citicoline in dementia patients. This study recruited 40 patients who were distributed into 4 groups: (1) 10 healthy elderly subjects; (2) 10 patients with early-onset Alzheimer's disease; (3) 10 patients with late-onset Alzheimer's disease; and (4) 10 patients with multiinfarction dementia. These patients received treatment with citicoline at a dose of 1 g/d p.o. for 3 months. After this treatment period, all groups displayed significant improvements in MMSE scores (Figure 24) and a significant antidepressant effect, as assessed by the Hamilton scale for depression (Figure 25). Patients with early-onset Alzheimer's disease were found to have significantly higher interleukin 1β (IL-1β) plasma levels at baseline compared to all other groups, revealing the participation of a neuroimmune change in the pathophysiology of Alzheimer's disease. After citicoline treatment, IL-1β plasma levels were normalised, which suggests that this drug has a certain immunomodulatory action. In a subsequent phase of their study, this group showed that in patients with Alzheimer's disease, citicoline not only improved cognitive function but also improved cerebrovascular function, as assessed using transcranial Doppler ultrasonography [464]. The neuroimmune effect of the drug was demonstrated by the findings that citicoline therapy decreased histamine plasma levels that are abnormally elevated in patients with Alzheimer's disease [465] and increases the plasma levels of tumour necrosis factor alpha or TNFα [466].

This same group recently published the results of a double-blind, randomised, placebo-controlled, pilot study where citicoline (1 g/d/12 weeks p.o.) or placebo was administered to 30 patients with mild to moderate senile dementia of the Alzheimer type [467]. As compared to the 17 patients treated with placebo, patients receiving citicoline who had a positive APOE ε4 genotype showed a significant improvement in their cognitive capacity, as assessed with the ADAS scale ($p < 0.05$). As seen previously, citicoline was shown to increase cerebral blood flow and improve bioelectric activity in the brain.

Soto et al [468] showed the value of the therapeutic association of citicoline, piracetam and a dihydropyridine calcium channel blocker, either nicardipine or nimodipine, for the treatment of senile dementia of the Alzheimer type. Cacabelos et al [469] also advocated a multifactorial treatment that would include citicoline for Alzheimer's disease in genotyped patients for this disease.

In a systematic review published by the Cochrane Library, Fioravanti et al [470] examined the effects of citicoline in the treatment of cognitive, emotional and behavioural deficits associated with chronic brain disorders in the elderly. Fourteen studies were included in this review. Some of the included studies did not present numerical data that were suitable for analysis. The description of participants varied over the years, the type and severity of the disorders varied and the participants ranged from aged individuals with subjective memory disorders to patients with vascular cognitive impairment (mild to moderate), vascular dementia, or senile dementia (mild to moderate). Seven studies observed subjects for a period of 20-30 days, one study had a duration of 6 weeks, four studies used periods extending over 2 and 3 months,

Figure 24. Effects of citicoline on cognitive function assessed using the MMSE in healthy older subjects (control), patients with early-onset Alzheimer's disease (EOAD) or late-onset Alzheimer's disease (LOAD) and patients with multi-infarct dementia (MID). [a] $p < 0.02$; [b] $p < 0.01$.



one study observed continuous administration over 3 months and one study was prolonged, with 12 months of observation. The studies were heterogeneous in dose, modalities of administration, inclusion criteria for subjects and outcome measures. Results were reported for the domains of attention, memory testing, behavioural rating scales, global clinical impression and tolerability. The reaction time was used as a measure of attention, and results were obtained from seven of the included studies with a total of 790 subjects, 384 in the citicoline group and 406 in the placebo group. Using the standardised mean difference (SMD) and a fixed-effect model, the summary effect size was −0.09 (95% CI = −0.23 to 0.05), and there was little effect of CDP-choline on attention. The meta-analysis of memory tests from ten studies included a total of 924 subjects, 456 in the citicoline group and 468 in the placebo group. The size of the effect on memory was 0.38 (95% CI = 0.11-0.65], which was statistically significant. Using six studies that reported memory test results in 675 participants with cognitive deficits associated with cerebrovascular disorders, the meta-analysis of memory function revealed homogeneous results, and there was evidence of a statistically significant positive effect on memory (SMD = 0.22; 95% CI = 0.07-0.37). Behaviour was measured using five different scales in eight studies with 844 subjects, 412 in the citicoline group and 432 in the placebo group. There was evidence of a positive effect of citicoline on behaviour (SMD = −0.60; 95 CI = −1.05 to −0.15) using the random-effects model. The evidence of benefit from global impression was stronger using a fixed-effect model, and the Peto odds ratio for improvement in subjects treated with citicoline as opposed to subjects treated with placebo was 8.89 (95% CI = 5.19-15.22). The finding that citicoline tended to be associated with fewer adverse effects than the placebo was relevant, but this finding was not statistically significant. According to the authors, further research with citicoline should focus on longer-

term studies in subjects who have been diagnosed with currently accepted standardised criteria, especially for vascular mild cognitive impairment or vascular dementia.

There are many studies on the use of citicoline for the treatment of cognitive disorders and dementia, and all have shown that this drug induces improvements in cognitive and behavioural improvements. Deutsch et al [471] are studying the association of citicoline plus galantamine in schizophrenia. The drug may be more effective for mild cognitive disorders [452-454,472,473] and cases of chronic cerebral vascular disease [474,475]. In addition, citicoline has beneficial effects on neurophysiological and neuroimmune changes.

Other clinical experiences

Parkinson's disease

Although levodopa continues to be the central therapeutic agent in Parkinson's disease, it has well-known limitations, the main limitation being a progressive loss of efficacy that is often evident after 3-5 years of treatment. Therefore, it seems warranted to use other drugs that can be administered in association with levodopa to allow for a decrease in the dosage of levodopa or even administered as the only medication in the early stages of the disease. The use of citicoline has been tested for this purpose because of its previously analysed capacity to increase dopamine availability in the striatum and act as a dopaminergic agonist. Citicoline is effective in various experimental models, and its use in Parkinson's disease is therefore accepted [476].

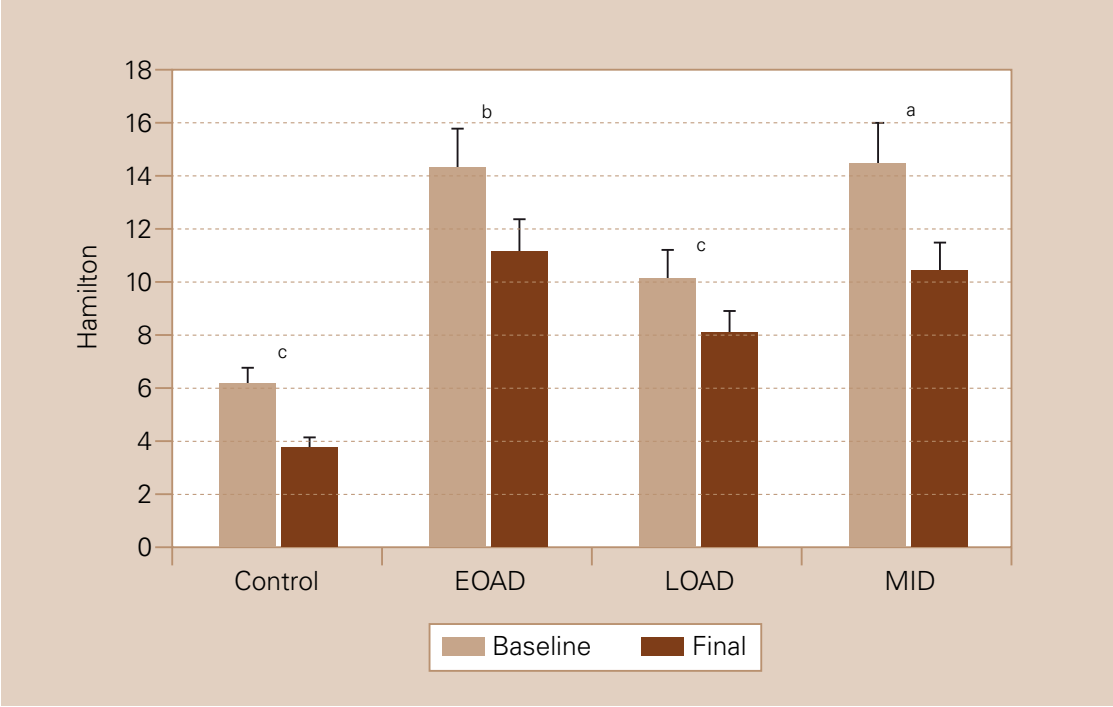
In a double-blind crossover study conducted on 28 Parkinsonian patients comparing 600 mg/d/10 d i.v. citicoline to a placebo, Ruggieri et al [477] showed that citicoline is an effective treatment for these patients by achieving improvements in assessments of bradykinesia, rigidity and tremor and in scores of the Webster scale and the Northwestern University Disability Scale (NUDS). The same investigators later obtained similar results in an extension of the aforementioned study [478]. They subsequently tested the effects of citicoline in two groups of patients with Parkinson's disease [479]. The first group included 28 patients who had not previously received treatment, and the second group included 30 patients who were already receiving treatment with levodopa and carbidopa for at least 2 months before the study and in whom the dosage had been stabilised at the minimum effective level. The same methods were used as in previous studies by these investigators, that is, a double-blind crossover study comparative to a placebo. Treatment was administered for 20 days at a dose of 500 mg/d by a parenteral route. Clinical assessments were performed on days 10 and 20, coinciding with the change in treatment, according to the study design. Treatment with citicoline provided statistically significant improvements in the Webster scale, NUDS and the assessment of bradykinesia in both patient groups. Rigidity also improved in both groups, although this improvement only reached statistical significance in the previously treated group of patients. Tremor also improved in both groups, but statistical significance was not reached.

Eberhardt et al [480-482] showed that combining citicoline with levodopa treatment allows a 50% reduction in the dose of levodopa, minimising the side effects associated with levodopa therapy. Thus, for this group of investigators, citicoline represents a useful alternative in patients requiring a reduction in levodopa doses and, moreover, the addition of citicoline to a treatment with levodopa may relieve decompensation states in the course of parkinsonism [483].

Loeb et al [484] conducted a multicentre, double-blind study with citicoline for the treatment of Parkinsonian patients. In this study, 65 patients were randomised to a group to which citicoline 1 g/d i.v. was added to their treatment or to a placebo group. Treatment lasted 21 days. All patients continued their underlying treatments with levodopa plus mianserin or benserazide for at least 8 weeks. The authors found significant differences between citicoline and the placebo after 14 and 21 days of treatment in all parameters assessed by the Webster and NUDS scales. They also noted that patients treated with citicoline experienced significant worsening 45 days after the medication was discontinued, thus showing the efficacy of citicoline as an adjuvant treatment to levodopa in patients with Parkinson's disease.

Acosta et al [485] treated 61 Parkinsonian patients with citicoline. Out of 61 patients, 48 were already receiving treatment with levodopa. Each patient received two treatment courses. In the first 10-day phase, 500 mg citicoline was administered daily by intramuscular injection. The first phase of the treatment was followed by a second phase of oral treatment at the same dose for 14 weeks. Patients treated with levodopa continued taking this medication at the same dose in the first period, after which an attempt was made to decrease it. Parkinsonian symptoms were assessed using the Webster

Figure 25. Antidepressive effects of citicoline in healthy older subjects (control) and in patients with Alzheimer's disease or multi-infarct dementia (MID), evaluated with the Hamilton Depression Scale. EOAD: early-onset Alzheimer's disease; LOAD: late-onset Alzheimer's disease. [a] $p < 0.02$; [b] $p < 0.01$; [c] $p < 0.05$.



scale. Among the patients receiving levodopa, 36% improved when citicoline was added, with greater percent improvements obtained in bradykinesia, rigidity, posture, gait and limb sway. In patients who had been treated with levodopa for less than 2 years, percent improvements amounted to 42.12%, compared to 19.08% of improvements in patients with more than 2 years of levodopa therapy. Levodopa doses could be decreased by 20-100% in 35.3% of patients with less than 2 years of treatment. In patients with more than 2 years of levodopa treatment, levodopa dose could be reduced by 25-33% in 10% of the cases. The authors concluded that citicoline treatment allows for delaying the start of levodopa therapy in the early disease stages and for decreasing or maintaining the levodopa dosage in previously treated subjects.

Cubells and Hernando [486] tested citicoline in 30 parkinsonian patients who were already being treated with levodopa. The dose administered was 500 mg/d by intramuscular injection for 2 months and was reduced to a third at the end of the first month of treatment. Changes in parkinsonian symptoms, according to the Yahr scale, were evident after the first month of treatment. Moderate improvements in facial expression and digital skills and obvious improvements in postural stability, motor changes and bradykinesia were observed. A greater stabilisation of the therapeutic response was also seen, with a decreased incidence of 'wearing-off' and 'on-off' phenomena, although dyskinesia increased. When the levodopa dose was decreased during the second study month, clinical improvements were maintained and the incidence of dyskinesia was decreased. Measurements of various electrophysiological parameters using an original technique revealed recovery from hyporeflexia and hypotonia after one month of treatment with citicoline. The authors found a major improvement in active muscle contraction, decreased muscle fatigue and an obvious recovery of contractile speed, a parameter that was greatly decreased before the

start of citicoline treatment. The authors stated that the increase in levodopa plasma levels was so significant that it could not be interpreted as due only to the increased release of dopamine stored in presynaptic vesicles. Therefore, they assumed that citicoline exerts an action on the synthetic mechanism of dopamine, acting through the tyrosine hydroxylase enzymatic system. In addition, the increase in dopamine receptors that were quantified in lymphocytes suggests, according to the authors, a promoting role of citicoline on the availability of postsynaptic dopamine receptors.

Martí-Massó and Urtasun [487] examined the effects of citicoline in 20 parkinsonian patients treated with levodopa for more the 2 years. These patients were administered 1 g/d/15 d i.m. citicoline and then continued with 500 mg/d for 15 additional days. Progressive improvements in symptoms was achieved. Thus, 4.16% and 7.26% overall improvements were achieved in the Columbia University scale at 15 days and at the end of treatment, respectively. The partial improvements that were achieved in ambulation, turning time in bed and writing time should be noted. In assessments conducted by relatives, improvements in agility, ambulation and general patient status deserve special mention.

García-Mas et al [488] conducted a study with quantified electroencephalography (qEEG) using fast Fourier transforms in two groups of patients with idiopathic Parkinson's disease, one of which showed cortical cognitive impairment. A study of specific qEEG indices allowed the establishment of some parameters that differentiate patients with and without cortical impairment. Specifically, differences were found in global potencies of delta and alpha rhythms, the alpha/theta index, posterior activities, anteriorisation index of delta and alpha rhythms and finally, spatialisation index of alpha rhythm. The administration of 2 g i.v. citicoline in these patients achieves a global increase in potencies corresponding to posterior rhythms, particularly the alpha rhythm, which is a marker of cognitive activity in dementia processes.

Based on the aforementioned studies, it may be stated that citicoline represents an effective treatment for Parkinson's disease in both untreated patients and patients who have already been treated with levodopa, in whom it also allows a reduction in the dose of levodopa. In patients with Parkinson's disease and cognitive impairment, citicoline administration induces a trend toward normalisation of the main altered electrophysiological parameters.

Alcoholism and drug addiction

Clinical experience with citicoline in alcoholism and drug addictions is not extensive, but there is some evidence of its efficacy in these applications.

Chinchilla et al [489] conducted a randomised double-blind study on the effects of citicoline in 20 patients with alcohol withdrawal syndrome. At the end of the study (at 2 months), there were significant improvements in attention-concentration and time and space orientation in the group of patients receiving citicoline. According to the authors, this finding suggests that the drug may be useful for treating chronic alcoholism.

Renshaw et al [490-492] published a double-blind pilot study of patients addicted to cocaine showing that after 14 days of treatment with 500 mg/12 h of citicoline or a placebo, the patients in the citicoline group experienced reductions in cravings for cocaine. Consequently, citicoline appears to be a promising therapy for this type of affliction. Furthermore, positive effects have been reported in patients with memory problems related with the use of cocaine [493]. There is a clear implication for cerebral metabolism in drug addiction pathophysiology [494,495]. There are also data suggesting the potential usefulness of citicoline in modulating appetite [496].

Amblyopia and glaucoma

There is clinical evidence that citicoline improves the visual acuity of patients with amblyopia [497-503] and visual function in patients with glaucoma [504-509] or non-arteritic ischaemic optic neuropathy [510].

Safety

Dinsdale et al [511] administered citicoline or a placebo to 12 healthy volunteers in two oral regimens that were repeated at short-term intervals (600 mg/day and 1 g/day) every day for 5 days. The only adverse effects that appeared were self-limiting headaches in four and five subjects with high and low doses, respectively, and in one subject who was given the placebo. The results of haematological and clinical analyses showed no abnormality associated with citicoline administration. No clinically significant ECG and EEG abnormalities were registered. Empirical neurological tests, tendon reflexes, blood pressures and heart rates were not affected by any dose of the drug or placebo.

In addition to excellent tolerability in healthy individuals, as demonstrated in the aforementioned study, all of the authors of the clinical trials using

Table XII. Safety analysis in the pooling data analysis of acute ischaemic stroke patients treated with citicoline. The table shows adverse events that were reported in more than 5% of cases. n.s.: no significative.

	Placebo		Citicoline		
	n	%	*n*	%	*p*
Adverse events with incidence > 5% in the citicoline group					
Anxiety	58	9.95	108	13.69	0.036
Leg oedema	38	6.52	77	9.76	0.032
Adverse events with incidence > 5%					
Accidental injury	86	14.75	135	17.11	n.s.
Agitation	78	13.38	113	14.32	n.s.
Constipation	228	39.11	286	36.25	n.s.
Coughing	81	13.89	105	13.31	n.s.
Diarrhoea	81	13.89	117	14.83	n.s.
Dizziness	46	7.89	72	9.13	n.s.
ECG abnormality	57	9.78	74	9.38	n.s.
Fever	182	31.22	241	30.54	n.s.
Auricular fibrillation	65	11.15	92	11.66	n.s.
Headache	186	31.90	261	33.08	n.s.
Haematuria	53	9.09	91	11.53	n.s.
Hypertension	88	15.09	131	16.60	n.s.
Hypokalemia	71	12.18	119	15.08	n.s.
Hypotension	55	9.43	90	11.41	n.s.
Urinary tract infection	235	40.31	298	37.77	n.s.
Insomnia	103	17.67	145	18.38	n.s.
Joint pain	48	8.23	78	9.89	n.s.
Nausea	111	19.04	157	19.90	n.s.
Pain	180	30.87	227	28.77	n.s.
Back pain	45	7.72	74	9.38	n.s.
Chest pain	55	9.43	82	10.39	n.s.
Rash	79	13.55	112	14.20	n.s.
Restlessness	49	8.40	74	9.38	n.s.
Shoulder pain	75	12.86	105	13.31	n.s.
Vomiting	89	15.27	111	14.07	n.s.
Adverse events with incidence > 5% in the placebo group					
Depression	160	27.44	178	22.56	0.038
Falling down	109	18.70	99	12.55	0.002
Urinary incontinence	82	14.07	83	10.52	0.047

citicoline that have been reviewed in this article agree in rating the safety of this drug as excellent and without serious reported side effects. In some cases, the appearance of digestive intolerance and occasional excitability or restlessness have been reported in the first days of treatment. For instance, Lozano [512] monitored a study of the efficacy and safety of citicoline in 2,817 patients of all ages, with a predominance of patients between 60 and 80 years who had different neurological conditions, mostly cognitive disorders of diverse origin. The duration of citicoline treatment ranged from 15 to 60 days, and the mean dose administered was 600 mg/day orally. Only 5.01% of the patients had collateral effects associated with citicoline treatment, most often digestive intolerance (3.6%). In no case was it necessary to interrupt treatment due to the side effects attributable to citicoline use.

In the pooled analysis of citicoline in the treatment of acute ischaemic stroke [390], there were few adverse events that were reported in more than 5% of patients in the safety analysis. These adverse events are listed in Table XII.

In the South Korean drug surveillance study [395], the safety of the product was considered excellent, with only 37 side effects in 31 cases among 4191 patients treated, giving a rate of 0.73%.

In addition, in the Cochrane Library review [470], a lower incidence rate of adverse events was demonstrated related to citicoline compared to placebo.

In conclusion, the tolerability of citicoline is excellent, and the side effects that are attributable to this drug are rare. The side effects are never severe and consist mainly of gastrointestinal discomfort and restlessness.

Conclusions

Cytidine 5'-diphosphocholine, CDP-choline, or citicoline is an essential intermediate in the biosynthetic pathway of structural phospholipids in cell membranes, particularly phosphatidylcholine. Following administration by both oral and parenteral routes, citicoline releases its two main components, cytidine and choline. Absorption by the oral route is virtually complete, and bioavailability by the oral route is approximately the same as by the intravenous route. Once absorbed, citicoline is widely distributed throughout the body, crosses the blood-brain barrier and reaches the central nervous system (CNS), where it is incorporated into the membrane and microsomal phospholipid fraction. Citicoline activates the biosynthesis of structural phospholipids of neuronal membranes, increases brain metabolism and affects the levels of different neurotransmitters. Thus, citicoline has been experimentally shown to increase norepinephrine and dopamine levels in the CNS. Owing to these pharmacological mechanisms, citicoline has a neuroprotective effect in hypoxic and ischaemic conditions and improves learning and memory performance in animal models of brain ageing. In addition, citicoline has been shown to restore the activity of mitochondrial ATPase and membrane Na^+/K^+ ATPase, to inhibit activation of phospholipase A_2 and to accelerate reabsorption of cerebral oedema in various experimental models. Citicoline is a safe drug, as shown by toxicological tests, that has no significant systemic cholinergic effects and is a well-tolerated product. These pharmacological characteristics and the action mechanisms of citicoline suggest that this product may be indicated for the treatment of cerebral vascular disease, head injury of varying severity and cognitive disorders of different causes. In studies conducted in the treatment of patients with head injuries, citicoline accelerated recovery from post-traumatic coma and improved gait, achieving an improved final functional outcome and shortening hospital stays in these patients. Citicoline also improved the mnesic and cognitive disorders seen after head injuries of minor severity that constitute the so-called postconcussional syndrome. In the treatment of patients with acute ischaemic cerebral vascular disease, citicoline accelerates the recovery of consciousness and motor deficit, achieves a better final outcome and facilitates the rehabilitation of these patients. The other major indication for citicoline is the treatment of senile cognitive impairment, secondary to either degenerative diseases (e.g., Alzheimer's disease) or either chronic cerebral vascular disease. In patients with chronic cerebral ischaemia, citicoline improves scores in cognitive rating scales, whereas in patients with senile dementia of the Alzheimer type, it stops the course of the disease and neuroendocrine, neuromodulatory and neurophysiological benefits have been reported. Moreover, citicoline has been shown to be effective as adjuvant therapy in Parkinson's disease. No serious side effects have occurred in any series of patients treated with citicoline, which attests to the safety of this treatment.

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Citicolina: revisión farmacológica y clínica, actualización 2010

Resumen. Esta revisión se basa en la publicada en el año 2006 –Secades JJ, Lorenzo JL. *Citicoline: pharmacological and clinical review, 2006 update.* Methods Find Exp Clin Pharmacol 2006; 28 (Suppl B): S1-56– e incorpora las nuevas referencias aparecidas desde entonces, con lo que se organiza toda la información disponible para facilitar el acceso a dicha información en un único documento. La revisión se centra en las principales indicaciones del fármaco, como son los accidentes cerebrovasculares agudos y sus secuelas, incluyendo el deterioro cognitivo, y los traumatismos craneoencefálicos y sus secuelas. Se recogen los principales aspectos experimentales y clínicos en estas indicaciones.

Palabras clave. Alcoholismo. Ambliopía. Apoptosis. CDP-colina. Citicolina. Demencia senil. Drogodependencia. Edema cerebral. Enfermedad de Alzheimer. Enfermedad de Parkinson. Fosfatidilcolina. Fosfolipasa. Fosfolípidos estructurales. Glaucoma. Ictus. Isquemia cerebral. Lesión cerebral traumática. Membrana neuronal. Memoria. Neuroplasticidad. Neuroprotección. Neurorreparación. Neurotransmisión. Trastorno cognitivo. Traumatismo craneoencefálico.