Citicoline: Update on a Promising and Widely Available Agent for Neuroprotection and Neurorepair

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Choline precursors promote repair and growth of cell membranes and hold promise in a variety of neurologic diseases, including ischemic and hemorrhagic stroke. Citicoline, the most well-studied choline agent precursor, is widely prescribed throughout the world and recently became available in the United States as a dietary supplement. In experimental stroke models, citicoline conferred acute neuroprotection and enhanced neuroplasticity and neurorepair in the subacute period. Although individual human stroke trials have been inconclusive, meta-analysis of 10 trials enrolling 2279 patients suggests patients receiving citicoline had substantially reduced frequencies of death and disability. Reinvestigation of citicoline with modern neuroimaging and clinical trial methods are underway and will provide more definitive information regarding the mechanistic and clinical effects of this promising neurotherapeutic agent.
[Rev Neurol Dis. *2008;5(4):167-177*]

Key words: Citicoline • Intracerebral hemorrhage • Ischemic stroke • Neuroplasticity • Neuroprotection

Damage to cell membrane integrity is an important mediator of cell death in a variety of neurologic diseases. Because phospholipid molecules are essential constituents of cell membranes in all mammals, treatments to protect and regenerate phospholipids are a promising strategy in clinical neurotherapeutics. Choline precursors are exogenous agents that are converted to choline in the body and promote the maintenance, repair, and de novo formation of cell membrane phospholipids, as well as the neurotransmitters acetylcholine and dopamine; choline precursor agents include choline, lecithin, choline alphoscerate, and citicoline. Of these, citicoline has shown the greatest

promise as a neuroprotective and neuroreparative agent. Oral choline is metabolized by intestinal bacteria to a highly volatile amine that is excreted in urine, sweat, and breath, and produces an unpleasant fishy odor, limiting its use in humans. Lecithin has been tested in numerous small trials in patients with dementia, including vascular dementia, but has not been subjected to large, high-quality randomized trials. This review of citicoline focuses on its potential application in acute and subacute stroke, where it has been most extensively tested, and briefly surveys studies of the agent in diverse other neurologic disease states.

Citicoline is an essential intermediate in the synthesis of structural phospholipids of cell membranes and has been the focus of sustained neuroscientific laboratory study and neurologic clinical trial investigation for more than 4 decades.[1] Two events make review of this potential neuroprotective and neuroreparative agent especially timely. In 2004, the dietary supplement industry began marketing citicoline in the United States, making it directly available to American patients and physicians for the first time.[2] In 2006, a large phase III trial of citicoline in acute stroke was launched to conclusively confirm or disconfirm the tantalizing—but not definitive—evidence of benefit observed in prior trials.[3]

Few agents developed for neurologic conditions have as extensive a record of observations on humans as citicoline. In formal clinical trials, citicoline has been studied in more than 11,000 volunteers and patients. Moreover, although only recently made available as a dietary supplement in the United States, citicoline has long been marketed as a prescription drug abroad. Citicoline is currently available by prescription in over 50 countries on 6 continents, including Europe (Spain, France, Russia), the Americas (Mexico, Brazil, Argentina), Africa and the Middle East (Algeria, Jordan, Iraq), and Asia (Japan, China, South Korea).

Mechanism of Action

Also known as cytidine diphosphocholine (CDP-choline), citicoline is a mononucleotide composed of ribose, cytosine, pyrophosphate, and choline (Figure 1). Oral doses of citicoline are absorbed rapidly and then hydrolyzed in the intestinal wall and liver to choline and cytidine. These enter the systemic circulation, cross the blood–brain barrier, and recombine to form citicoline within the central nervous system.

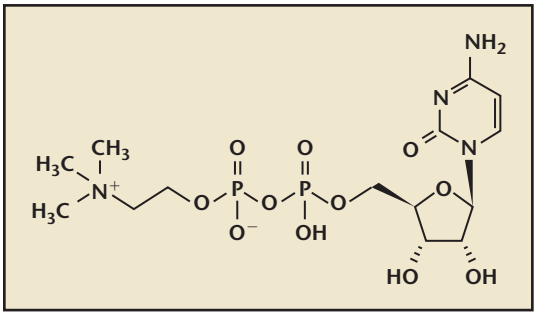

Figure 1. *Chemical structure of citicoline (cytidine diphosphocholine [CDP-choline]). Reprinted with permission from Secades JJ and Lorenzo JL.*[1]

Acute neuroprotection by citicoline in brain ischemia was first described in experimental studies 3 decades ago.[4] Two leading mechanisms have been suggested to mediate the neuroprotective effect observed when citicoline is administered within the first hours of onset of cerebral ischemia: 1) direct repair of neuronal membranes, and 2) reduced generation of free fatty acids (FFAs).

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Neuronal Membrane Repair

Phospholipids are the essential constituents of cell membranes and required for maintenance of homeostasis, activity of membrane associated enzymes, coupling of receptor and intracellular signaling, and nerve impulse conduction. The main phospholipids in humans are phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and sphingomyelin. The synthesis of 80% of central nervous system phospholipids can be controlled by altering the concentration of citicoline.[5] Exogenously administered citicoline promotes rapid repair of injured cell surface and mitochondrial membranes and maintenance of cell integrity and bioenergetic capacity. Citicoline downregulates phospholipases to avert apoptotic and necrotic cell death.[6,7]

Decreased Free Fatty Acid Accumulation

In ischemic neurons, cellular energy failure and ATP depletion produces breakdown of membrane phosphatidylcholine to FFAs. FFAs mediate

additional tissue injury. FFAs are metabolized to toxic oxygenated metabolites and free radicals and also uncouple mitochondrial oxidative phosphorylation. Experimental studies have demonstrated that exogenous citicoline administration stimulates phosphatidylcholine synthesis and attenuates FFA release. In addition, citicoline stabilizes lipid rafts that carry glutamate transporter proteins, thereby increasing the removal of excitotoxic glutamate neurotransmitter from synaptic clefts.[8]

The neuroplasticity enhancing and neurorestorative effects of citicoline in the subacute period days to weeks after onset have been suggested to be mediated by 2 additional leading mechanisms: 1) accelerated synthesis of membrane phospholipids, and 2) enhanced production of the neurotransmitter acetylcholine.

Synthesis of Membrane Phospholipids

Cell membrane phospholipids have a very high turnover rate; continuous synthesis of replacement compounds is required to maintain cell integrity in normal circumstances. Even greater demand for phospholipid generation arises during the subacute poststroke period to support neurogenesis, axonal sprouting, and synaptogenesis. Formation of citicoline is the rate-limiting step in the formation of phosphatidylcholine through the Kennedy cycle. Exogenously administered citicoline accelerates phospholipid synthesis and neural repair. Among animals treated with citicoline in the subacute stroke period, motor recovery was greater and motor neurons structurally showed enhanced dendritic complexity and spine density, suggesting that choline precursor therapy increased neuroplasticity within noninjured regions, mediating functional recovery.[9]

Neurotransmitter (Cholinergic and Dopaminergic) Production

Acetylcholine is a neurotransmitter that mediates learning and memory and multiple additional nervous system functions. Injury to cholinergic transmission pathways with decreased release of acetylcholine is an important contributor to cognitive deficits after stroke. Citicoline serves as a choline donor in the biosynthesis of acetylcholine. In animal stroke models, administration of citicoline increases the release of acetylcholine at cholinergic nerve endings and improves attentional, learning, and memory performance. Dopamine is a neurotransmitter involved in movement, attention, and diverse other functions. Citicoline increases dopamine synthesis, likely via enhancing tyrosine hydroxylase activity, inhibiting dopamine reuptake at nerve terminals.

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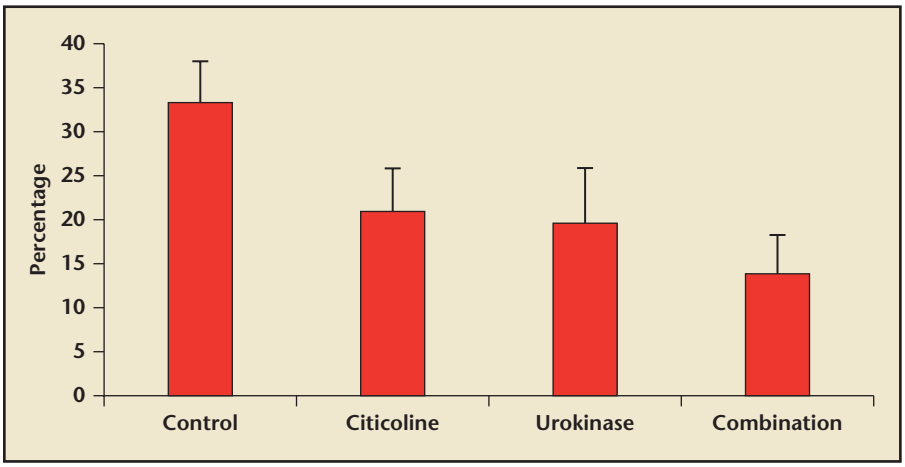
Synergies With Recanalization and Neuroprotective Therapies

As a neuroprotective and neurorestorative agent, citicoline has the potential to complement recanalization therapies. Delivered before achievement of recanalization by pharmacologic fibrinolysis or endovascular device, citicoline could enable more threatened tissue to survive until revascularization relieves ischemic stress. Administered in the early period after recanalization, the agent could attenuate reperfusion injury. In the subacute poststroke period, citicoline could enhance the neurorepair and restoration function provided by tissues preserved by reperfusion. In several animal stroke model studies, coadministration of citicoline and fibrinolytics (including tissue plasminogen activator and urokinase) increased the reduction in infarct size attained by the fibrinolytic alone (Figure 2).[10,11]

Figure 2. *Infarct volume (as a percentage of hemisphere volume) among animals with embolic middle cerebral artery infarctions under control conditions and after treatment 2 hours after onset with a citicoline bolus, a urokinase thrombolytic bolus, and a combination of citicoline and urokinase. Error bars represent standard deviations. Data adapted with permission from Shuaib A et al.[10]*



Similarly, preclinical studies suggest that citicoline can complement other neuroprotective drugs to more fully stabilize the ischemic penumbra or block reperfusion injury. By inhibiting a wider array of molecular pathways that elaborate cell injury in hypoxic environments, combinations of neuroprotective drugs have the potential to be more effective than single agents. In rodent stroke models, administration of citicoline has potentiated the reduction in infarct size achieved by excitotoxity inhibitors (MK-801),[12] presynaptic sodium channel inhibitors (lamotrigine),[13] and calcium channel blockers (nimodipine).[14] Citicoline may also add to the benefits of other agents with neuroplasticity-enhancing effects: citicoline coadministration with a nerve growth factor (fibroblast growth factor) yielded greater benefits than either agent alone.[15]

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Basic Pharmacology and Toxicity

When infused intravenously in humans, citicoline is rapidly hydrolyzed to choline and cytidine for delivery to tissues throughout the body. In healthy volunteers, at the end of a 30-minute infusion, plasma levels of citicoline are already virtually undetectable, whereas choline and cytidine levels are at a peak, with continued elevated circulating concentrations for the following 6 hours. Though not as rapid as intravenous (IV) administration, oral administration also provides an efficient means of delivery, with choline and cytidine plasma levels peaking 2 hours after a single oral dose. Passage across the blood–brain barrier is efficient. Radioactive tracer studies in rats show that, after IV administration of radioactively labeled citicoline, labeled phospholipid concentrations in the brain increase steadily over the next 10 hours and remain high at 48 hours. Exogenous citicoline achieves wide distribution throughout the brain. In a mouse study, 24 hours following administration of labeled citicoline, the tracer was widely incorporated in cortex, white matter, and central gray nuclei. Eventual elimination of administered citicoline occurs very slowly, with small amounts exiting each day by the urinary, fecal, and respiratory routes.

Citicoline exhibits a very low toxicity profile.[1] In preclinical studies, a lethal oral dose could not be determined because no deaths occurred at the maximum possible oral dose. No toxic effects were observed in 30-day subacute and 6-month chronic administration toxicity studies of oral citicoline in rodents and dogs. No changes occurred in blood chemistry, organ histology, or neurological or urinary parameters. In humans, in multiple formal clinical trials with prospective monitoring, no categories of serious adverse events have been reported to have an increased frequency in active study arms. Uncommon nonserious adverse effects include gastrointestinal distress, restlessness, and irritability, generally within the first few days of treatment. A large drug surveillance study analyzed the safety profile of citicoline in 2817 patients, predominantly elderly individuals treated for Alzheimer and vascular dementia, with treatment duration ranging from 2 to 9 weeks. Only 5% of patients reported adverse effects; gastrointestinal distress was most common (3.6%), and no patient needed to discontinue therapy due to side effects.

Clinical Trials in Acute and Subacute Stroke

Stroke is a leading cause of adult disability and the second leading cause of human mortality, accounting for 10% of all deaths worldwide. A total of 13 randomized clinical trials of citicoline in acute and subacute stroke have been reported in the literature. Three of these trials reported positive results but did not present global outcome data details permitting amalgamation with other studies. Formal meta-analysis could be undertaken of the remaining 10 trials, enrolling a total of 2279 patients. The characteristics of these trials are shown in Table 1. The studies fall generally into 4 categories. In the early 1980s, 3 relatively small-sized European studies, predominantly in ischemic stroke, were reported from single centers. In the late 1980s, 1 moderate-sized multicenter study in ischemic stroke was performed in Japan. In the late 1990s and early 2000s, 4 moderate- to large-sized multicenter studies in ischemic stroke were conducted in the United States. In the past several years, 2 moderate-sized multicenter studies have investigated citicoline in intracerebral hemorrhage (ICH).

The timing and routes of therapy application in the completed trials are noteworthy; 9 of the 10 trials, enrolling 99% of the patients,

Table 1
Design Feature of Trials of Citicoline in Acute and Subacute Stroke

Study	Year	Size (N)	Stroke Type	Maximal Permitted Time From Onset	Citicoline Daily Dose and Delivery Mode
Boudouresques and Michel[29]	1980	45	CVA	48 h	750 mg IV × 10 d
Goas JY et al.[30]	1980	n/a	Ischemic stroke (not CT confirmed)	24 h	750 mg IV or IM × 10 d, then 250 mg IV or IM × 10 d
Corso EA et al.[31]	1982	33	CVA	10 d	1000 mg IV × 30 d
Tazaki Y et al.[17]	1988	272	Ischemic stroke	14 d	1000 mg IV × 10 d
Clark WM et al.[18]	1997	257	Ischemic stroke	24 h	1) 500 mg PO × 6 wk; 2) 1000 PO mg × 6 wk; 3) 2000 PO mg × 6 wk
Clark WM et al.[19]	1999	394	Ischemic stroke	24 h	500 mg PO × 6 wk
Warach S et al.[16]	2000	100	Ischemic stroke	24 h	500 mg PO × 6 wk
Clark WM et al.[20]	2001	898	Ischemic stroke	24 h	2000 mg PO × 6 wk
Secades JJ et al.[21]	2006	33	Intracerebral hemorrhage	6 h	2000 mg PO or IV bid × 2 wk
Chua R[22]	2007	183	Intracerebral hemorrhage	24 h	4000 mg IV × 2 wk

bid, twice daily; CT, computed tomography; CVA, cerebrovascular accident; IM, intramuscular; IV, intravenous; n/a, not available; PO, by mouth.

permitted late enrollment of patients up to 24 hours to 14 days after onset. Though not stated, it is likely that very few patients enrolled in these trials received the study agent within the first 3 hours of symptom onset, when acute neuroprotective effects would be most potent. Therapy was begun orally in 4 trials enrolling 72% of all studied patients, with initial IV or intramuscular initiation only in a few small trials. As oral administration delays achievement of potentially neuroprotective levels, likely irreversible infarction had developed in much of the tissue at risk in patients enrolled in these trials prior to arrival of substantial amounts of study agent in nervous system tissues. Conversely, therapy was continued for a long duration in all trials, with courses of 10 days to 6 weeks, affording a substantial time period for neuroreparative agent effects to accrue.

From a modern drug development perspective, the 10 trials can be divided into 7 small phase II trials and 3 large phase III trials. In the phase II trials, study goals included dose optimization, detection of biologic activity, demonstration of safety, and identification of signals of potential efficacy. Appropriately for these diverse goals, the primary prespecified endpoints of the phase II trials varied widely.

Among the phase II trials, the Citicoline 010 trial (C010)[16] holds a special place in the history of stroke trial design as the first randomized trial to analyze infarct evolution on magnetic resonance imaging (MRI) as its prespecified primary endpoint. Use of multimodal MR or computed tomography indices of penumbral salvage to provide direct evidence of drug activity is now commonplace in proof of concept trials for

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neuroprotective and reperfusion agents. The C010 trialists obtained serial images of lesion volume pretreatment, at week 1, and at week 12, permitting separate analysis of early lesion growth and late lesion contraction. The natural history of cerebral infarcts is to grow to a maximum at 1 week because of early, transient swelling from cytoxic edema, and then contract to a substantially smaller volume at 3 months due to tissue atrophy from cell loss. Neuroreparative agents, in contrast to acute neuroprotective drugs, may not reduce the initial growth in infarct volume, but rather increase the neural reorganization and repair in perilesional zones, an effect better interrogated by functional MRI, MR spectroscopy, or late evolution of infarct volume. On the C010 trial prespecified primary outcome measure, among 81 enrolled patients, a trend was noted to reduced growth in infarct volume between pretreatment and week 12 images in the citicoline group (11.3 mL vs 18.9 mL; $P = .18$). Intriguingly, in the C010 trial, citicoline did not attenuate the volume of infarct growth in week 1 (28.4 mL vs 25.7 mL) but did enhance the volume of lesion reduction between week 1 and week 12 (−17.2 mL vs −6.9 mL; $P < .01$), perhaps indicating a late neuroreparative effect as perilesional tissue more vigorously filled in the infarct cavity.

The first pivotal phase III trial of citicoline in ischemic stroke was performed in Japan in the 1980s. The Japanese cooperative trial was placebo controlled and blinded, had 63 participating centers, and assigned 272 patients to low-dose citicoline (500 mg daily) or placebo for 14 days.[17] Entry criteria permitted patients to be enrolled up to 14 days after stroke onset and more than two-thirds of the enrolled patients started study therapy on poststroke day 3 or later, making this primarily a trial of citicoline's subacute neurorepair effects, rather than acute neuroprotection. The trial authors reported they found beneficial effects, with moderate or greater improvement on the Japanese Coma Scale present in 51% of citicoline patients vs 33% of placebo patients ($P < .01$). This result certainly is suggestive, but interpretation of the clinical significance of the finding is hampered by the method and timing of outcome measurement. The clinical outcome of focal strokes is best assessed by measures of focal neurologic deficit, functional disability, social handicap, and experiential quality of life, but none of these were directly indexed by the trial's level of consciousness scale. Also, the final outcome assessment occurred in the first month after stroke onset, at a time when neurologic recovery is still actively under way, rather than at 3 months or later, when the final outcome has generally been achieved.

In the late 1990s and early 2000s, the US Citicoline Stroke Study Group[18-20] performed several multicenter trials, enrolling patients within 24 hours of the time stroke deficits were first observed. In a preliminary dose response trial, both low (500 mg daily) and high (2000 mg daily), but not medium (1000 mg daily), doses were found to produce a beneficial shift toward better functioning levels on the Barthel Index of functional disability.[18] The group then performed an efficacy trial of the low-dose regimen in a 33-site study that randomized 394 patients to low-dose citicoline (500 mg) or placebo for 6 weeks.[19] This trial showed no difference in prespecified outcomes. However, the study was handicapped by an imbalance in prognostic factors among randomized patients, with placebo-treated patients having milder strokes at enrollment.

The same study group then performed the largest trial of citicoline yet reported. A consortium of 118 centers assigned 899 patients to high-dose citicoline (2000 mg daily) or placebo for 6 weeks, with final outcome assessments at 12 weeks.[20] Although outcomes on the unusual primary and secondary endpoint analyses prespecified by the trialists were neutral, beneficial effects or trends were observed on a variety of outcome analyses more standard in the field. For example, a nondisabled outcome at 3 months was achieved by 41% of citicoline-treated patients versus 35% of placebo-treated patients ($P = .05$).

The most recent trials of citicoline in subacute stroke are noteworthy for being the first trials of a neuroprotective/neuroreparative agent to focus upon ICH rather than ischemic stroke patients. In a pilot, double-blind, randomized trial conducted at 4 Spanish academic hospitals, 38 patients were randomized within 6 hours of symptom onset to high-dose (2000 mg daily) citicoline or placebo for 2 weeks, with final outcome assessments at 3 months.[21] Safety was suggested by equal rates of mortality and/or recurrent brain hemorrhage in the 2 groups. A signal of potential efficacy was noted in an on-treatment analysis that excluded patients failing to complete the 14-day treatment regimen, with a nondisabled outcome (modified Rankin score [mRS] 0-2) achieved by 28% of citicoline-treated patients versus 7% of placebo-treated patients (odds ratio [OR] 5.4, 95% confidence interval [CI], 0.6-52.4). However, substantial imbalance in entry neurologic deficit severity (citicoline group median 9 vs placebo 15) renders efficacy analysis unreliable. In a

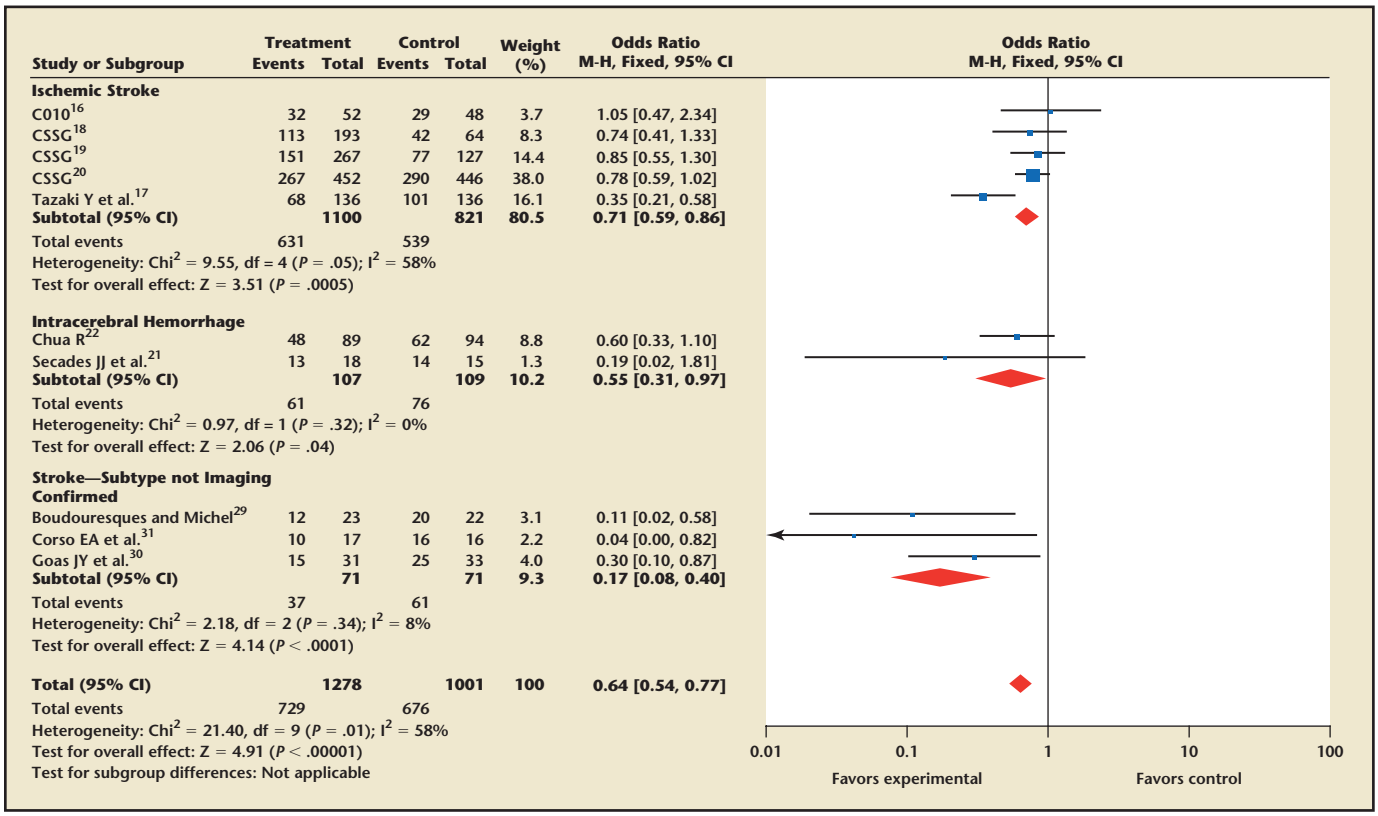
larger 6-center trial in the Philippines (the Role of Intravenous Citicoline for Supratentorial Hemorrhage trial),[22] 182 supratentorial ICH patients were randomized within 24 hours of onset to very high-dose citicoline (4000 mg daily) or placebo for 14 days. Rates of nondisabled outcome (mRS 0-2) at 3 months trended higher in the citicoline-treated group (46.1% vs 33.8%, OR 1.71, 95% CI, 0.94-3.11; $P = .11$).[22] Demonstrating that citicoline is at least safe, and possibly beneficial, in ICH would permit the drug to be administered early after onset, at home or in the ambulance, prior to brain imaging. Indeed, in some localities in Spain, prehospital personnel now administer IV citicoline to acute stroke patients in the field, prior to hospital arrival, as an element of routine clinical practice.

Meta-Analyses

All of the citicoline trials in acute stroke performed to date were underpowered to detect a modest, but clinically worthwhile, benefit. Their variable results, with some trials positive and others neutral on their primary endpoints, and some of those neutral on primary endpoints being positive on secondary endpoints, raise the possibility that citicoline exerts a beneficial effect that none of the completed trials, considered singly, was large enough to reliably detect. The possibility that citicoline confers a modest treatment benefit has been further explored by combining the results of individual small trials via meta-analysis. Both study-level and individual patient-level meta-analyses of citicoline in focal stroke suggest a treatment benefit.

A study-level meta-analysis of the 10 reported trials is shown in Figure 3, updating an earlier report.[23] Among the 2279 patients enrolled across all trials, assignment to citicoline rather than placebo was associated with a substantial reduction in the frequency of death or disability at long-term follow-up (57.0% vs 67.5%, OR 0.64, 95% CI, 0.54-0.77; $P < .00001$). However, there is substantial scatter among the trials, with smaller, lower-quality score trials tending to show more highly favorable

Figure 3. *Death or dependency at long-term follow-up. Forest plot meta-analysis of effect of citicoline versus control in trials enrolling patients with ischemic stroke, intracerebral hemorrhage, 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 Saver JL. Citicoline Update. UCLA Stroke Center Lecture Series; September 25, 2008.*



effects than larger, higher-quality score trials (test for heterogeneity, $P = .01$). An analysis confined to the 4 largest ($N > 100$) ischemic stroke patient trials yields a homogenous group of well-reported trials, and finds a smaller, but still highly significant, treatment effect: choline precursors 574/1048 (54.8%) versus placebo 500/773 (64.7%) (OR 0.70, 95% CI, 0.58-0.85; $P = .0003$). In a safety analysis, data across all trials reporting mortality outcomes on deaths by end of trial follow-up show no adverse effect of citicoline: citicoline 179/1235 (14.5%) versus placebo 135/966 (14.0%) (OR 0.99, 95% CI, 0.77-1.21; $P = .94$). This study-level analysis has advantages of comprehensiveness and of following standard meta-analysis guidelines, but cannot take into account individual patient variability.

The Citicoline Steering Committee sought to maximize the probability of identifying a beneficial effect of citicoline by pooling individual patient level data from across the 4 US trials, including only those patients with baseline characteristics rendering them likely to be able to demonstrate a response to an efficacious agent.[24] Key criteria limiting the study population included requiring a substantial neurologic deficit at the time of study enrollment (National Institutes of Health Stroke Scale [NIHSS] ≥ 8) and a high functioning prestroke status (mRS 0-1), and removed 17% of the patients enrolled in the 4 trials from the pooled analysis. The primary endpoint examined was that employed in the pivotal National Institute of Neurological Disorders and Stroke tissue plasminogen activator (NINDS-tPA) trials,[25] global recovery at 3 months as indexed by minimal residual neurologic deficit (NIHSS 0-1), minimal residual impairment on activities of daily living (Barthel Index ≥ 95), and minimal residual global disability (mRS 0-1). Global recovery occurred more often with citicoline than placebo (OR 1.3, 95% CI, 1.1-1.6; $P < .004$). Full recovery on all 3 measures simultaneously was achieved by 25.2% of citicoline-treated patients versus 20.2% of placebo-treated patients. Safety analyses were generally favorable. Anxiety and leg edema occurred slightly more often in patients assigned to citicoline, whereas depression, falls, and urinary incontinence occurred slightly more often in patients assigned to placebo.

The possibility that citicoline exerts a modest but worthwhile benefit that trials performed thus far have not been adequately powered to detect is further highlighted by comparing treatment effects across the entire range of outcomes between citicoline and tPA, a well-established therapy of proven benefit when administered within 3 hours of onset. Comparing the largest trials of the 2 agents (the 2 NINDS-tPA trials and the Citicoline Stroke Study Group 2001 trial), the magnitude of the treatment effect across the entire range of clearly valued disability outcomes for citicoline is about two-fifths that of early thrombolytic therapy. For every 100 patients treated in less than 3 hours with tPA, 30 benefit and 2 are harmed; for every 100 patients treated within 24 hours with citicoline, 12 benefit and none are harmed (J.L. Saver, unpublished data, 2008).

The International Citicoline Trial on Acute Stroke

The results of these formal meta-analyses are encouraging, suggesting a moderate but real benefit of choline precursor therapy in acute and subacute stroke. However, beneficial effects identified only in meta-analysis are best treated as hypotheses, not conclusions, and require prospective confirmation in subsequent large trials. The International Citicoline Trial on acute Stroke (ICTUS) was launched in November 2006 to accomplish this goal. ICTUS is a multicenter trial currently under way in Spain, Portugal, and Germany, and is assigning 2600 acute ischemic stroke patients within 24 hours of onset to high-dose citicoline (2000 g daily) or placebo, with treatment started intravenously for the first 3 days and continued orally until 6 weeks. As of May 2008, 550 patients had been enrolled at 39 sites.[3] Several of the lessons of design infelicities in past trials have been applied to the design and conduct of ICTUS. ICTUS is large enough to ensure detection of moderate treatment effects. The sample size of ICTUS alone is larger than all 8 prior ischemic stroke trials combined. ICTUS is enrolling only patients with more severe presenting neurologic deficits, avoiding mild deficit patients destined for excellent outcome with supportive care alone, who are uninformative regarding intervention effects. The initially enrolled patient population in ICTUS has substantially more severe deficits (median NIHSS 17) than patients enrolled in prior trials (median NIHSS 11-13). Patients are being treated earlier in ICTUS, and treatment is started intravenously, affording an opportunity for citicoline to exert acute neuroprotective as well as subacute neuroreparative effects. The median time from onset to treatment among initially enrolled patients is 4.5 hours.

There are certainly aspects of the ICTUS design with which one may quibble. The use of binary extreme excellent outcomes to compose the primary endpoint is more appropriate for an early recanalization agent than for a neuroprotective/neuroreparative agent and may lessen study power. Given citicoline's

potential short-term symptom relief effects as a neurotransmitter enhancer (which differs from its potential long-term structural cure effects as a neuroreparative agent), adding assessments on the last day of drug administration at 6 weeks to the current post-washout evaluations at 12 weeks would more fully probe for all types of potential benefits the agent may confer. The 2600 patient sample size, although large, could still miss a potential clinically relevant benefit. With its safety, affordability, and ease of administration, citicoline would lend itself well to a megatrial enrolling 10,000 patients and using an extremely simple 1-page case report form, and would be more certain to detect beneficial effects. However, it is clear that ICTUS will constitute a powerful (and likely final) test of citicoline in acute stroke, confirming or disconfirming the tantalizing suggestions of benefit from prior trials.

Other Neurologic Conditions

As loss of neuronal and glial membrane integrity is a final common pathway of cell injury arising from many disease processes, citicoline has been tested in a wide variety of neurologic conditions aside from focal stroke.

Late-Life Cognitive Impairment

Most directly relevant to stroke are studies in patients with late-life cognitive impairment that have preponderantly targeted patients with vascular cognitive impairment or mixed vascular and Alzheimer disease. Several small trials have been conducted, but their interpretation is challenging. Some trials have sought to enroll only patients with vascular cognitive impairment and vascular dementia, but others have investigated solely Alzheimer disease patients or less well-defined cohorts with "senile dementia." The most recent Cochrane review of these studies identified 14 trials enrolling a total of 1051 patients and concluded that there was some evidence of a positive effect upon memory, behavior, and global functioning, though not on attention.[26] Additional trials using modern, standardized diagnostic criteria for patient selection were recommended.

Head Trauma

Dating back to the 1960s, several small cohort studies and randomized trials have investigated citicoline in traumatic brain injury, ranging from traumatic coma to postconcussion syndrome. Studies reported in the literature generally suggest benefits of therapy, including accelerated resolution of cerebral edema, earlier recovery of consciousness, shorter hospital stay, greater motor and memory recovery, and improved quality of life. However, the reported studies are generally single center and not stringently designed, making interpretation perilous.

Main Points

- Damage to cell membrane integrity is an important mediator of cell death in a variety of neurologic diseases. Choline precursors are exogenous agents that are converted to choline in the body and promote the maintenance, repair, and de novo formation of cell membrane phospholipids, as well as the neurotransmitters acetylcholine and dopamine. Of the choline precursor agents studied, citicoline has shown the greatest promise as a neuroprotective and neuroreparative agent.
- Citicoline exhibits a very low toxicity profile. In preclinical studies, a lethal oral dose could not be determined because no deaths occurred at the maximum possible oral dose. No toxic effects were observed in 30-day subacute and 6-month chronic administration toxicity studies of oral citicoline in rodents and dogs. In formal clinical trials in over 11,000 individuals, no major safety concerns have been identified.
- Phospholipids are the essential constituents of cell membranes and are required for maintenance of homeostasis, activity of membrane associated enzymes, coupling of receptor and intracellular signaling, and nerve impulse conduction. The synthesis of 80% of central nervous system phospholipids can be controlled by altering the concentration of citicoline.
- Reinvestigation of citicoline with modern neuroimaging and clinical trial methods is underway and will provide more definitive information regarding the mechanistic and clinical effects of this promising neurotherapeutic agent. Collectively, the data from the 10 randomized clinical trials of citicoline in stroke patients, enrolling 2279 patients, suggests potential benefit. A study-level meta-analysis of all 10 trials indicates that citicoline reduced the rate of death or disability at late follow-up from 67.5% in placebo-treated patients to 57% in citicoline-treated patients ($P < .00001$).
- In human clinical stroke trials, citicoline has generally been administered relatively late after onset (1-14 days) and continued for extensive time periods (typically 6 weeks)—a dose schedule that emphasizes potential neurorepair enhancement effects and minimizes potential acute neuroprotective effects.

Parkinson Disease

Citicoline increases dopamine production in the striatum and has shown benefits in a variety of experimental models of Parkinson disease. Several small open-label and controlled clinical trials performed in the 1970s and 1980s suggested potential benefits of citicoline in Parkinson patients. However, large trials incorporating current design principles are lacking.

Glaucoma and Ischemic Optic Neuropathy

Glaucoma may in part be mediated by ischemic injury to retinal and postretinal structures due to elevated ocular tension. Small controlled trials using visual electrophysiologic endpoints have suggested a beneficial effect of citicoline. Nonarteritic ischemic optic neuropathy is a chronic, small artery–mediated ischemic injury to the intraocular optic nerve. A recent randomized but open-label trial in 26 patients found improved visual acuity and visual evoked potentials in citicoline-treated patients when compared with control subjects.[27]

New Directions

Citicoline has been tested in and prescribed to humans for over 40 years. Over this long period, it has acquired an impeccable record of safety, but like many agents whose first testing antedates modern clinical trial methodology, incomplete evidence of benefit. From the 1960s to the 1990s, many pioneering but loosely performed trials suggested potential benefit in a variety of neurologic conditions. In the 1990s, a series of moderate-sized, better organized trials suggested, but did not unequivocally demonstrate, benefit in acute and subacute stroke. Viewed from a current clinical translational research perspective, multiple potentially fruitful approaches await application to this promising agent. To probe whether citicoline enhances beneficial reorganization and remapping of motor and cognitive functions after initial injury, studies using functional MRI, voxel-based morphometry, diffusion tensor imaging, and MR spectroscopy would be of great interest.[28] To determine whether citicoline exerts an acute neuroprotective effect, a subacute neuroreparative effect, or both, a 2 × 2 trial separately randomizing patients to hyperacute and subacute therapy would provide explanatory insight. As citicoline is a very safe agent, it is an excellent candidate agent for a prehospital trial evaluating its administration in the first 1 to 2 hours after stroke onset, testing whether it can increase the amount of penumbra that is available for salvage when recanalization therapies are later delivered after hospital arrival. It is time to pour old wine into new bottles, and determine if citicoline is genuinely a useful agent to protect and repair the nervous system in stroke and other neurologic conditions. ■

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