Emerging Therapy Critiques

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Poststroke Pharmacotherapy

Another Ictus

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The term ictus, used medically to denote a stroke or seizure, is a Latin word meaning “a blow.” Unfortunately, this definition is also an appropriate descriptor of the International Citicoline Trial on Acute Stroke (ICTUS)—its results are another blow to the search for a safe and effective pharmacological approach for augmenting the clinical benefit of acute reperfusion therapy in patients with ischemic stroke or improving outcomes for those who cannot be recanalized. This carefully designed and conducted, multicenter, double-blind, randomized trial found that, “citicoline is not efficacious in the treatment of moderate-to-severe acute ischemic stroke,” (primary outcome for intention-to-treat with citicoline based on a global outcome statistic including the National Institute of Health Stroke Scale, modified Rankin score, and Barthel index; odds ratio, OR=1.03, 95% CI, 0.86–1.25). 1

Although referred to as a new drug in the ICTUS report, experimental and clinical data related to citicoline’s putative mechanisms of action and potential therapeutic effects have accrued over the last 4 decades. 2,3 Exogenous citicoline (cytidine-5'-diphosphocholine) is hydrolyzed to cytidine and choline, phosphorylated, and then resynthesized by cytidine triphosphate-phosphocholine cytidyltransferase. 4 Citicoline is the rate limiting intermediate for the synthesis of phosphatidylcholine, an important membrane phospholipid. 4 Although brain levels of citicoline after parenteral or oral administration are unknown, about 0.5% of total radioactivity of orally administered radiolabeled citicoline is incorporated into brain tissue compared with about 2% of an intravenous dose. 5

In contrast to acute reperfusion interventions such as pharmacological thrombolysis or mechanical clot retrieval, treatment with citicoline had the potential to improve stroke outcomes through both neuroprotective (aimed at reducing the extent of ischemic injury) and neurorestorative (approaches affecting brain plasticity during the recovery process) effects. Neuroprotective actions of citicoline are hypothesized, at least in part, to be mediated through an attenuation of phospholipase A2 activation, preserving mitochondrial membrane cardiolipin, increasing phosphatidylcholine levels, raising glutathione synthesis and glutathione reductase activity, decreasing lipid peroxidation, and improving Na+\(^{+}/\)K+–ATPase activity. 5 Neurorestorative actions may facilitate neural repair and postinjury neuroplasticity in addition to having effects on neurotransmitters such as acetylcholine and dopamine. 6

Even before ICTUS, citicoline had been studied in >11 000 patients and volunteers. 1 The theoretical benefits for patients with ischemic stroke were supported by a patient-level pooled-analysis of data from 4 randomized trials (n=1372) that showed a treatment-associated one-third improvement in 3-month outcomes (OR=1.33; 95% CI, 1.10–1.62; P=0.0034), 2 and a study-level meta-analysis of 5 trials (n=1921) showing a 29% reduction in long-term death or disability (OR=0.71, 95% CI, 0.59–0.86). 2 No single high-quality trial was positive, prompting ICTUS, which was intended to confirm the results of the pooled, individual patient analysis, but failed to do so. Although 24% of subjects included in the ICTUS intention-to-treat analysis had various protocol violations, there also was no benefit in the per-protocol population (OR=1.05, 95% CI, 0.84–1.31). There was no treatment effect for the intention-to-treat or per-protocol populations based on a secondary shift analysis of the modified Rankin score and no effect for any of the individual outcome scales.

Several recent secondary stroke prevention trials have failed, at least in part, because of lower than expected event rates in the control population, likely because of general improvements in preventive care. 4 ICTUS was not a secondary prevention study, but review of masked data during the course of the trial indicated better than expected subject outcomes. This difference between the expected and observed rates of good outcomes might be attributed to several factors, including high rates of treatment with intravenous tissue plasminogen activator (tPA) (46%), as well as general improvements in poststroke care. The ICTUS Data Safety Monitoring Board recommended increasing the study sample to restore power to 80%. Nonetheless, recruitment was stopped because of futility after the third of 4 planned interim analyses (complete data for 2078 subjects of 3350 planned); no safety issues were identified. Stopping a trial before planned enrollment is completed because of unexpected serious complications or an imbalance in adverse events is critical to ensure that patients are not placed at undue risk. Stopping prematurely for futility, incorporated into the protocol of modern phase III clinical trials, saves resources and spares subject and investigator time and effort, but results in a study that is ultimately underpowered for testing its primary hypothesis. Given the reported neutral results of ICTUS, it is very unlikely that the conclusion would have been different had the full, planned study population been enrolled.

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Subjects could be randomized in ICTUS within 24 hours of symptom onset (79% were randomized within 12 hours). Given that at least part of citicoline’s putative effect is based on neuroprotection, even a 12-hour treatment window may have been too long.\(^3\) In addition, although citicoline (or its metabolites) cross the blood-brain barrier and the drug was initially administered intravenously to enhance brain tissue levels, its neuroprotective effects might have been limited by low penetration into ischemic brain, especially in the setting of a persistent occlusion. In experimental studies, the effect of citicoline in reducing infarct size is greater in models of transient as compared with permanent arterial occlusion.\(^3\) ICTUS subjects who were treated with intravenous tPA would be expected to more commonly have been reperfused and, therefore, have relatively higher penetration of citicoline into ischemic tissue, thereby increasing the likelihood of a neuroprotective effect. A post hoc exploratory analysis included in the ICTUS report (which should be considered as hypothesis generating, especially because the primary trial result was neutral) suggested the opposite; there was heterogeneity based on whether the subject was also treated with intravenous tPA (intention-to-treat, interaction \(P=0.0413;\) per-protocol \(P=0.0956),\) but favoring the control rather than the citicoline-treated group. Although chance or imbalances between the subgroups treated or not treated with tPA might explain this heterogeneity, the finding is unexpected. Clinically more than balanced by the benefits of early reperfusion, experimental studies indicate that tPA may have neurotoxic effects that could increase infarct volume through a variety of mechanisms, including increasing blood-brain barrier permeability and potentiation of apoptosis.\(^10–12\) It is conceivable that citicoline’s neuroprotective effects might have been diminished by the neurotoxic effects of tPA, or that the neurotoxic effects of tPA were in some way potentiated by citicoline. tPA may also induce matrix metalloproteinase-9, thereby increasing the risk of hemorrhagic complications.\(^13\) There was, however, no evidence that citicoline increased this effect as there was not a higher rate of intravenous tPA-associated asymptomatic or symptomatic intracerebral hemorrhage in those who were also treated with citicoline.

Even if the long time window, limited citicoline levels in ischemic brain tissue, or other factors obviated its neuroprotective effects, as noted, citicoline has properties that might enhance neurorestorative processes. Experimental studies show that postbrain-injury neuroplasticity and associated functional motor recovery are strongly affected by motor experience.\(^14\) Consistent with these findings, clinical physiotherapeutic interventions can have an important impact on functional outcome.\(^15\) Novel approaches such as constraint-induced movement therapy can lead to long-lasting and clinically important improvements in arm function after stroke.\(^16\) High-intensity automated repetitive practice (robotic therapy) also holds promise.\(^17\) The effects of training and practice may be augmented pharmacologically, but the behavioral impact of putative neurorestorative drugs may require that their administration be carefully timed to maximize these interactions.\(^18\) For example, the Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME) trial found that the administration of fluoxetine combined with physiotherapy improved motor recovery after 3 months.\(^19\) Other drugs affecting central neurotransmitters, when combined with training, may also modulate the recovery process.\(^20\) Most clinical acute stroke trials, including ICTUS, do not control or account for the potential effects of poststroke physiotherapy or the use of other drugs that might affect functional recovery, and ICTUS did not require that a particular physiotherapeutic intervention be tied to drug administration.

The ICTUS study report included an updated meta-analysis of 6 trials (n=4219 with ICTUS representing over half the cases). Despite the neutral results of ICTUS, the OR for a modified Rankin score of 0 to 2 was 1.14 (95% CI, 1.00–1.30) with a fixed effect model (i.e., assuming a similar treatment effect among the studies). There was, however, statistical heterogeneity between the trials (\(P=0.003),\) with an early study conducted in Japan strongly favoring citicoline treatment. The OR for a random effects model (i.e., assuming the effects in individual studies vary around an overall mean) was somewhat higher, but no longer significant (OR 1.30, 95% CI, 0.96–1.76). If the single outlier study is excluded, statistical heterogeneity among the remaining studies is not significant (\(P=0.34),\) with a similar, non-significant treatment effects with both fixed effects (OR=1.07, 95% CI, 0.93–1.22) and random effects (OR=1.08, 95% CI, 0.93–1.27) models.

The potential reasons for the failure of ICTUS are varied, and much of this discussion, based on citicoline’s complex pharmacological actions, has been speculative. One wonders whether the chance of detecting a neuroprotective-related citicoline treatment benefit might have been greater had it been given sooner after symptom onset and before the administration of intravenous tPA. Would an effect on functional recovery been evident if drug administration was combined with tailored, intensive physiotherapy? Could preclinical testing specifically designed to evaluate these issues provided insights that might have informed the design of the trial? The stroke research and clinical communities have been disheartened by a long history of failed neuroprotective studies and a lack of proven pharmacological approaches to improve poststroke recovery. Although ICTUS represents another blow to these hopes, we should not yet abandon the concepts.

**Disclosures**

None.

**References**


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