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Citicoline in stroke and TBI clinical trials

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The results of recent citicoline trials by Dávalos *et al.*[1] and Zafonte *et al.*[2] showed that citicoline is not efficacious in treating stroke and TBI, respectively, a view that has been echoed by others,[3,4] including a recent News & Views article in this journal (Stroke: Treatment for acute stroke—the end of the citicoline saga. *Nat. Rev. Neurol.* 8, 484–485; 2012).[5] Studies in rodent models of stroke, however, have indicated that bioavailability of this drug may be an issue that has been repeatedly overlooked in the clinical trials, making it premature to conclude that citicoline is ineffective. Our and others' research with animal models strongly suggests that if a liposome formulation had been used, the reported results from the clinical trial would have been different.[6–9]

Route of administration, bioavailability and metabolism of citicoline are vital factors in stroke and TBI clinical trials. On the basis of absorption and excretion, bioavailability of citicoline is believed to be the same between oral and intravenous routes. Animal studies have shown, however, that brain uptake of citicoline is greater with the intravenous route than with the oral route.[7] Citicoline metabolism in humans differs from that in rodents: in rodents, citicoline administration increases blood plasma levels of cytidine and choline, while in humans blood plasma levels of uridine but not cytidine are increased due to cytidine deaminase in the gastrointestinal tract and liver.[10] In both humans and rodents, citicoline is metabolized to choline and cytidine triphosphate (CTP) by the liver; after passing through a compromised blood–brain barrier (BBB) these two components need to be reassembled by rate-limiting CTP:phosphocholine cytidylyltransferase (CCT), which is downregulated after stroke. Downregulation of CCT and upregulation of phospholipases result in significant phosphatidylcholine loss,[11,12] and the therapeutic action of citicoline is thought to be due to stimulation of phosphatidylcholine synthesis.[13]

BBB breakdown after stroke allows passage of citicoline liposomes directly through the compromised vasculature,[6,7] and the intact drug will be delivered to the brain, thereby circumventing the rate-limiting CCT.[11] Citicoline liposomes (intravenously administered) in animal stroke studies are effective at low doses[6] and have prolonged circulation time; in addition, brain uptake is ~23%, compared with 2% for the standard (unencapsulated citicoline) intravenous route and 0.5% for the oral route.[7] Future clinical trials of citicoline should, therefore, consider the above factors, including liposomal formulation for testing. Citicoline is a relatively safe and nontoxic agent with minimal adverse effects, and an appropriate route of delivery and formulation may have positive effects on stroke and TBI outcomes.

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Competing interests
The author declares no competing interests.

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