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Citicoline: Mechanisms and Stroke Clinical Trials

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We read with interest the article on citicoline phase III clinical studies [1]. The therapeutic action of citicoline is thought to be due to stimulation of phosphatidyl-choline (PtdCho) synthesis in the injured brain, though evidence is unclear [2]. In this regard, Figure 1 needs correction. The biosynthesis of PtdCho from 1,2- diacylglycerol (diglyceride) and CDP-choline forms cytidine 5'- monophosphate as the other product, not monoacylglycerol (monoglyceride).

Our studies in transient cerebral ischemia suggest that citicoline might enhance reconstruction (synthesis) of PtdCho and sphingomyelin, but could inhibit the destructive processes (activation of phospholipases). [2-5] Citicoline neuroprotection may include: preserving cardiolipin and sphingomyelin; preserving arachidonic acid content of PtdCho and phosphatidylethanolamine; partially restoring PtdCho levels; and stimulating glutathione synthesis and glutathione reductase activity. The effects of citicoline could be explained by the attenuation of phospholipase A_2 activation and also to a singular unifying neuroprotective mechanism of this drug [2].

The following points may need to be considered in future clinical trials:

Patients were admitted into the clinical studies up to 24 hours after onset of symptoms, a longer timeframe than is used in most clinical trials. [1] Our studies indicate that citicoline does not provide neuroprotection if the onset of treatment is delayed by 3 hours. Another factor is the percentage of citicoline that is incorporated into the brain. As noted, all of clinical trials outside the US used IV administration in contrast to the oral route in US trials. It is generally believed that bioavailability is the same between oral and IV methods, but this conclusion was apparently based on absorption and excretion, not delivery of citicoline to the brain. [6] Animal studies have shown brain uptake of citicoline (or its metabolites) of only 0.5% with oral dose, which increased to ~2% when administered. IV Liposome encapsulation of citicoline increased brain uptake of the drug to 23% of the administered dose. [7]

In addition, citicoline metabolism in humans differs from rodents. In rodents, citicoline administration increases blood plasma levels of cytidine and choline. In humans, blood plasma levels of uridine but not cytidine are increased due to cytidine deaminase in the gastrointestinal tract and liver.[8]. It is believed that uridine must then enter the brain, become phosphorylated to uridine triphosphate, and then converted to cytidine triphosphate.

It may be necessary to combine citicoline with another agent targeted to a different pathway due to the multiple mechanisms contributing to ischemic brain injury.

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