REVIEW ARTICLE

Role of Citicoline in Ischaemic Stroke

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Introduction

Stroke or cerebrovascular accident is the third commonest cause of death, and the leading cause of long term disability in the world. Stroke is the clinical designation for a rapidly developing loss of brain function due to an interruption in the blood supply to all or part of the brain. This phenomenon can be caused by thrombosis, embolism, or haemorrhage. Stroke is represented predominantly by ischaemic stroke (80%) in which there is a loss of cerebral blood flow owing to vascular occlusion. The remaining 20% of strokes result from cerebral haemorrhage (1,2).

The incidence of stroke is expected to rise dramatically with the increasing ageing population. The risk of stroke doubles for each decade after age of 55. Stroke is a major factor for late-life dementia that affects more than 40% of population over the age of 80. One in four men will have a disabling stroke by the age of 80 and one in five women by the age of 85. Approximately, 85% of strokes are caused by cerebral infraction and among these patients, 4% have a recurrent stroke and 10% die within first month (3). In the past few years, a large number of compounds that interfere with the biochemical mechanism that, mediate ischaemic brain injury have been demonstrated to be neuroprotective in preclinical models of stroke. However, all those drugs that survived safety profile trials and were studied in phase III clinical trails have so far failed to prove efficacy (4).

Many neuroprotective agents has been shown to be effective in experimental settings, but none so far improved clinical outcome of acute ischaemic stroke. Citicoline (CDP-choline), cytidine 5 – disphosphocholine) is a form of essential nutrient choline. Neuroportection by citicoline has been described since 1978 (5). This has been found to be the drug of choice due to its proven safety and efficacy in patients with stroke.

Citicoline

Citicoline is a complex organic molecule, that function as an intermediate in the biosynthesis of cell membrane phospholipids. CDP–choline (citicoline) is composed of ribose, pyrophosphate, cystosine (a nitrogenous base), and choline (6). Citicoline is found to be effective in the treatment of stroke (7). Endogenously, formation of citicoline is the rate-limiting step in the synthesis of phosphatidylcholine from choline. Exogenous citicoline which is hydrolyzed in the small intestine and readily absorbed as choline and cytidine, enters the various biosynthetic pathways that utilize citicoline as an intermediate. Citicoline thus has a sparing effect on systemic choline reserves, as well as inhibiting the breakdown of membrane phospholipids (8). Exogenously administered citicoline prevents, reduces, or reverses the effects of ischaemia and /or hypoxia to decrease and limit nerve cell damage, restore intracellular regulatory enzyme sensitivity, function and limit edema.

Mechanism of Action

Citicoline, a neuroprotective agent has been investigated as a therapy for stroke patients. Citicoline appears to reverse neuronal membrane pathology that occurs in cerebral ischaemia. Studies demonstrated the three postulated mechanisms that include repair of the neuronal membrane via increased synthesis of phosphatidylcholine, repair of damaged cholinergic neurons via potentiation of acetylcholine production, and reduction of free fatty acid buildup at the site of stroke-induced nerve damage (9). During ischaemia, phosphatidylcholine is broken down into free fatty acids, which in turn are used to generate radicals that potentiate ischaemic injury. The exogenous administration of citicoline has been shown to reduce cell membrane breakdown, leading to increased synthesis of phosphatidylcholine and decreased levels of free fatty acids (Fig 1). Studies have found that citicoline

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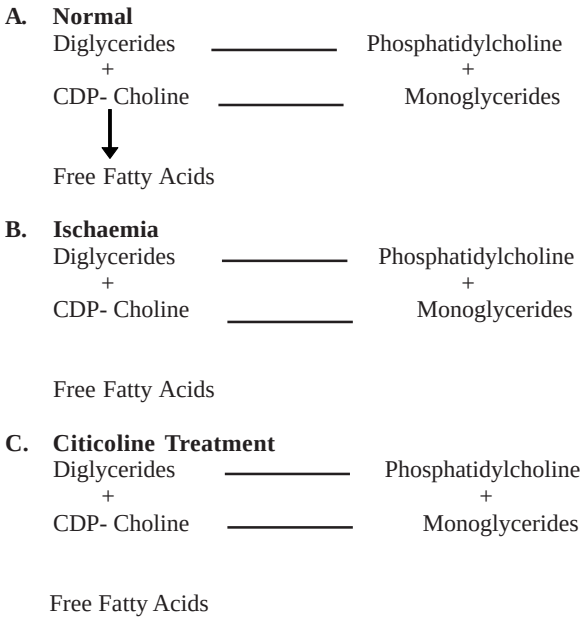
treatment decreases free fatty acids concentration improves neurological signs, decreases neurological deficits, preserves phosphatidylcholine levels and improves neuronal survival (8).In addition to phosphatidylcholine, citicoline also serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component. Citicoline has shown ability to restore post-ischaemic sphingomyelin levels (7). Citicoline also restores the levels of cardiolipin, a phospholipids component of the inner mitochondrial membrane.

Figure 1. (A) Diagrammatic Illustration of Normal Synthesis of Phosphatidylcholine. (B) Effect of Ischaemia on this Reaction. (C) Citicoline Treatment Reverse the Increased Fatty Acids Formation and Loss of Phosphatidylcholine



Clinical Trials

Numerous clinical trails performed over many years have documented the excellent tolerance and reliable efficacy of citicoline in patients with stroke.

Adibhatla *et al* (10) in a review of citicoline in stroke and other CNS disorders which included a total of 13 stroke clinical trails of citicoline (nine in Europe and Japan, four in the USA) showed that citicoline improved a global and neurological function and promoted earlier motor and cognitive recovery. A large multi center study from Japan found that citicoline showed improvement in a global outcome rating scale. Subsequently pooling of individual patient data from four US clinical trails showed that citicoline treatment for 6 weeks improved overall recovery at 12 weeks in acute ischaemic stroke patients. Pooled diffusion-weighted magnetic resonance imaging (DW-MRI) data from two clinical trails showed a significant dose dependent reduction in percent change in lesion volume.

The study by Davalos *et al* (11) evaluated the effects of oral citicoline in patients with acute ischaemic stroke by a data pooling analysis of clinical trials. The primary efficacy end point chosen was the common evaluation of recovery, combining National Institutes of Health Stroke Scale </=1, modified Rankin Scale score </=1, and Barthel Index >/=95 at 3 months using the generalized estimating equations analysis. A complete recovery was observed in 25.2%, citicoline-treated and 20.2% placebo-treated patient after 3 months treatment period. The overall safety of citicoline was similar to placebo. Thus, results of this study demonstrated that treatment with oral citicoline within the first 24 hours after onset in patients with moderate to serve stroke increases the probability recovery at 3 months.

In a multicenter, double-blind controlled trail (12) effect of oral citicoline was evaluated in patients with stroke. A total 259 patients were recruited and divided into 4 groups. Group 1 (n=65), group II (n=65) and group III (n=65 received a citicoline 500mg, 1000mg, and 2000mg, respectively, where as group IV (n=64) received a placebo within 24 hours after stroke onset. The treatment was continued for six weeks, with a six week follow-up period. The primary clinical end point was a change in the Barthel Index of Neurological Function.

The base line NIH stroke scale (NIHSS) score was assessed as second variable to decrease the effect of baseline difference in stroke severity. After 12 weeks, patients in the groups received 500mg or 2000mg citicoline were found to have twice chances of stroke recovery compared to placebo.Because the patients received 2000mg had a higher incidence of dizziness, researchers concluded that 500mg/d might be the optimum citicoline dose.

Bruhwyler *et al* (13) in a open-label study evaluated the efficacy and tolerability of citicoline in 123 subjects who had an acute stroke. The study was conducted for period of 14 days. During first 5 days, citicoline was administered intravenously (2g/d). From day 6, it was administered intramuscularly (1g/d). Patients were assessed on day 0, 3, 7 and 14 using the Canadian Neurological (CAN) scale, including the Glasgow Coma scale (GCS) and spontaneously side effects also recorded at each visit.

The total score on CAN ($p<0.0001$) and GCS ($p<0.012$) showed a significant evaluation over time. The results of this study demonstrated that citicoline is an effective and well tolerated treatment for patients suffering from acute cerebral infraction including acute stroke.

Clinical Safety

Citicoline has an excellent track record of clinical safety. A large drug surveillance study analyzed the results of citicoline treatment in 2,817 patients between age group 60-80 years suffering form senility and cerebral vascular insufficiency. A total of 151 incidents of side effects were recorded, representing five percent of the patient sample. The most common adverse effects were transient in nature and included stomach pain and diarrhoea in 102 cases. Vascular symptoms of hypotension, tachycardia, or bradycardia occurred in 16 cases (14,15).

Conclusion

Stroke or cerebrovascular accident is the third commonest cause of death and the leading cause of long-term disability in the world. Citicoline is a neuroprotective agent that serves as a choline donor and intermediate in the biosynthesis of phospholipids. Citicoline reduces ischaemic injury in the CNS by preserving membrane phospholipids, chiefly phosphatidylcholine. Citicoline is found to be a drug of choice due to its proven safety and efficacy in patients with stroke.However, the clinical experience will help to establish its clinical supermacy in the coming times.

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