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NEUROPROTECTION IN ACUTE STROKE: IS THERE STILL HOPE?

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SUMMARY – Efficacious treatment of acute stroke is a major challenge in modern medicine. Therapeutic neuroprotection acting towards minimization of ischemic neuronal injury in penumbral tissue in the regions of reduced cerebral blood flow seems to be an appealing concept in the treatment of acute stroke and brain trauma. The 'ischemic cascade', a complex mechanism of metabolic events initiated by brain ischemia, offers many pathways by which the neuroprotective agents may act. Time to treatment remains a major limiting factor for many potential neuroprotective agents. Although the exact therapeutic window is not known, evidence from many animal models and clinical research suggest that neuroprotective therapy can only be efficacious if administered very early after the onset of ischemia. Various neuroprotective agents have been tested in many clinical stroke trials during the past 20 years. Large phase III clinical trials of several classes of neuroprotectants (mainly NMDA receptor antagonists, free radical scavengers, and calcium channel blockers) have recently failed to demonstrate efficacy of neuroprotection. After initial disappointment, the active research continues and some new exciting neuroprotective models emerge on the horizon.

Key words: *Cerebrovascular accident, drug therapy; Clinical trial; Treatment outcome; Neuroprotective agents*

Introduction

Stroke is the most common neurological emergency encountered by physicians worldwide. It is only since the last decade that stroke has been recognized as an urgent condition. The concept of strokes as 'brain attacks' has gained wide popularity, and has motivated many basic and clinical researchers to search for its efficacious treatment. In the 'decade of the brain', many clinical trials of therapeutic agents for the treatment of acute brain attacks were conducted. An efficacious treatment of stroke is still a major challenge in modern medicine.

Clinical trials in stroke prevention have been more successful in demonstrating the benefits of treatment of stroke risk factors than from treatment of acute stroke itself. Anti-platelet agents in primary and secondary prevention of stroke, and carotid endarterectomy for secondary prevention of stroke are well established therapies. The early preventive measures and treatment for cerebrovascular disease have contributed to the decrease in the prevalence of overall mortality from both coronary artery disease and stroke[1].

A Window of Opportunity for Intervention

Brain ischemia initiates an 'ischemic cascade', a complex sequence of metabolic events from energy depletion, involvement of the generation of nitrogen and oxygen free radicals, through excitation of NMDA receptors and intracellular influx of calcium, to the induction of apoptotic and necrotic pathways. All of these mechanisms produce brain damage that occurs within few minutes to hours after transient brain ischemia, or in the penumbral region

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of infarcts after permanent ischemia. The mode of cell death that prevails probably depends on the severity, duration and precise nature of the ischemic injury. However, all of these metabolic events initiated by brain ischemia may be the potential sites of possible action of a neuroprotective agent.

The National Institute of Neurological Diseases and Stroke (NINDS) tissue plasminogen activator (tPA) stroke study has demonstrated the pivotal role of time as a limiting factor for the successful treatment of strokes[2]. Rodent models of acute middle cerebral artery occlusion consistently demonstrate that reperfusion within 3 hours of arterial occlusion can limit the size of the resulting infarct and improve other measures of outcome[3]. These studies also show that reperfusion after 3 hours has little benefit and may provoke the development of malignant cerebral edema with hemorrhagic transformation of the ischemic brain regions ('reperfusion injury')[4].

Time to treatment remains a major limiting factor with these animal models, demonstrating that neuroprotective therapy is only efficacious when initiated as a pretreatment or early after focal ischemia[2,3]. The exact therapeutic time window is unknown, but evidence suggests that infarct volume can only be reduced if neuroprotective measures are initiated within 1 to 2 hours from the onset of ischemia[5]. The rationale for combination therapy includes the inhibition of glutamate induced excitotoxicity, reduction or inhibition of potential neuronal toxic compounds such as nitric oxide or free radicals, and inhibition of apoptosis ('programmed cell death'), which are involved in altered neuronal and microglial gene structure and expression. These factors have an important deleterious effect on the 'reperfusion injury' that may be observed with thrombolysis. A strategic combination of neuroprotection and thrombolytic therapy may also prolong the 'window of opportunity'[5]. 'Time is brain', so is the underlying pathomechanism.

Neuroprotective Agents in Cerebral Ischemia

Therapeutic neuroprotection in acute ischemic strokes seems to be an appealing concept which may potentially increase the therapeutic window of opportunity for thrombolytic treatment. Large phase III clinical trials of several different neuroprotective agents including nimodipine and lubeluzole have, however, failed miserably (Table 1)[6-9].

The latest study of a neuroprotectant, gavestinel, in acute stroke was completed last year (GAIN Americas: Glycine antagonist in neuroprotection)[10]. In the press release on April 4, 2001, Dr. Ralph L. Sacco (New York), the principal investigator of the GAIN study, reported that stroke patients treated within 6 hours with an experimental drug, gavestinel, showed no improvement 3 months after stroke compared with placebo. This trial was the largest study of a neuroprotective agent for acute stroke in North America. "While the finding was a disappointment, in light of the growing belief that rapid action to counter the damage of acute stroke might improve outcomes for patients, the strategy of neuroprotective drugs to treat ischemic stroke still remains a significant area for investigation." The GAIN trial was a randomized, double-blind, placebo-controlled trial that enrolled 1,367 patients with acute ischemic stroke within 6 hours of onset at 132 hospital centers in the United States and Canada. Thirty-nine percent of the gavestinel treated patients were independent at 3 months, compared with 37 percent of the patients administered placebo. Even among 241 patients treated within 4 (rather than 6) hours of stroke onset, no beneficial effect for gavestinel was recorded. Neither was any benefit of gavestinel demonstrated among 333 patients treated with tPA. On the other hand, gavestinel had no serious side effects. This study corroborated the results of a similar study of gavestinel conducted in Europe, Australia and Asia (GAIN International)[11]. Dr. Sacco and his colleagues conclude that, while this agent was not efficacious, "we still believe neuroprotection remains a viable strategy for acute stroke treatment and should continue to be studied." Moreover, the completed trials have provided large evidence of safety data, allowing for some understanding of which agents may be well tolerated by stroke patients and continue to be investigated[12].

Although many researchers have lost their enthusiasm for neuroprotection, many more still think there is hope for neuroprotection, especially with better methods of conducting clinical trials. The long list of clinical trials that failed with neuroprotective agents have raised concerns about how to proceed best for the future development of such interventions. The Stroke Therapy Academic Industry Roundtable (STAIR) have published recommendations for standards of preclinical and clinical neuroprotective and restorative drug development[13,14]. This conference of academicians and industry representatives was convened to suggest guidelines for the preclinical and clinical evaluation of neuroprotective drugs, and to recommend to potential clinical investigators the data they should review to reassure themselves that a particu-

Table 1. Neuroprotective agents that proved a failure in clinical trials for acute stroke[*]

Mechanism of action	Agent
Antagonists of voltage sensitive calcium channels	Nimodipine
	Flunarazine
	Darodopine
Excitatory amino acid antagonists	Monoganglioside GM1
Noncompetitive antagonists of NMDA receptor	Dizocilipine maleate
	Aptiganel hydrochloride
	Dextrophan
	Dextromethorphan, HBr
Competitive antagonists of NMDA receptor	Selfotel
	Antagonists of AMPA receptors
	Antagonists of polyamine regulatory sites
	NBQX
	Eliprodil
	Ifenprodil
	CPPene, dCPPene
Antagonists of glycine regulatory sites	Gavestinel (GV150526)
Inhibitors of glutamate release	Lamotrigine
	BW 619 C89
Scavengers of free radicals	Tirilazid neylate
Antibody to intercellular leukocyte	Enlimomab
Enhancement of the effect of GABA-A receptors	Clomethiazole
Inhibition of nitric oxide synthetase	Lubeluzole
Growth factors	Basic fibroblast growth factor
Stabilization of neuronal membranes	Citicoline
Opioid antagonist	Nalmefene
	Naloxone

[*]Selection made from ref. nos. 6-9, 15, and Washington University Internet site: *University Stroke Trials Directory*

lar neuroprotective drug has a reasonable chance to succeed in an appropriately designed clinical trial. The most important points for clinical investigators to assess before considering embarking upon a trial of a new neuroprotective agent include an appropriate dose-response curve analysis, time window studies, proper blinded animal studies in preferably two species and reproducible treatment effect in two laboratories, and outcome measures with infarct volume and functional assessment. Without a rigorous, robust and detailed preclinical evaluation, it is unlikely that novel neuroprotective drugs will prove efficacious when tested in large, time-consuming and expensive clinical trials.

Most neuroprotectants act on one selected process in the ischemic cascade, which may not be sufficient to reduce brain damage as other processes continue. Current neuroprotective strategies target mainly ischemia induced excitotoxic mechanisms, ischemia induced nitric oxide associated neuronal damage, and ischemia associated neuronal cellular membrane damage (Table 2)[6-8,15]. Drugs that act at different levels of the ischemic cascade may be more powerful as neuroprotectants[15]. In the future, therapeutic neuroprotective strategies may also include agents that prevent apoptosis and other redundant neurotoxic mechanisms that become active with cerebral ischemia. A combination of several different neuroprotective agents that act on several steps in the excitotoxic cascade in the form of a 'stroke cocktail' has only theoretical advantages but it may also be a rational step forward for better treatment during the 'ischemic cascade' of events in acute

Table 2. Neuroprotective agents currently investigated in clinical trials for acute stroke[*]

Mechanism of action	Agent
Scavengers of free radicals	NYX 059
Noncompetitive NMDA antagonists	Magnesium sulfate
	AR-R 15896 AR
Agonists of serotonin (5HT1A receptor)	BAY 3702
Sodium channel blocker	Sipatrigine
Potassium channel blocker	BMS-204352 (MaxiPost)
Membrane activated calcium chelator	DP-b99
Neutrophil inhibitory factor (CD11b/CD18 receptor)	Corleukin (UK-279,276)
AMPA receptor antagonist	YM872 (in combination with tPA: ARTIST+)
Nitric oxide inhibitor	Glyceryl trinitrate
Membrane stabilizer	Piracetam
Early GABA-ergic activation	Diazepam
Recovery: Transplant LGE cells (porcine neuronal cells)	Diacrin

[*]Selection made from ref. nos. 6-9, and Washington University Internet site: *University Stroke Trials Directory*

stroke. Meanwhile, this concept is on hold as the Food and Drug Administration does not allow the use of a combination of two or more investigational drugs in clinical trials.

Currently, hypothermia and drugs with a potential to enhance recovery after acute ischemic stroke seem to be the most promising approaches. Randomized clinical trials of the effect of hypothermia (body surface cooling, or more recently endovascular cooling catheters) in acute stroke are just underway in many institutions[9]. Additionally, the STAIR recommendations have provided a set of overall guidelines for the development of drugs and interventions in the field with great potential but limited positive trials.

Conclusion

Time as well as complex pathophysiology continue to be the major limiting factors for the successful treatment of acute ischemic strokes. At present, thrombolytic therapy remains the only approved form of treatment for acute ischemic strokes. However, phase II and III trials of several neuroprotective agents that are currently underway give us hope that in the near future all patients with acute stroke will receive some form of intervention that may help limit the disability and devastation caused by stroke.

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Sažetak

NEUROZAŠTITA U AKUTNOM MOŽDANOM UDARU: IMA LI JOŠ NADE?

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Učinkovito liječenje akutnog moždanog udara velik je izazov u suvremenoj medicini. Terapijska neurozaštita kojom bi se ishemijsko neuronsko oštećenje u tkivu penumbre u područjima smanjenog moždanog krvnog protoka svelo na najmanju moguću mjeru čini se primamljivom zamisli u liječenju akutnog moždanog udara i moždane traume. 'Ishemijska kaskada', odnosno složen mehanizam metaboličnih događaja što ih potiče moždana ishemija, nudi mnoštvo putanja kojima bi neurozaštitna sredstva mogla djelovati. Vrijeme proteklo do početka liječenja ostaje glavnim ograničavajućim čimbenikom za mnoga potencijalna neurozaštitna sredstva. Iako točan terapijski prozor nije poznat, rezultati dobiveni u mnogobrojnim životinjskim modelima i kliničkim istraživanjima ukazuju na to da bi neurozaštitna terapija mogla biti učinkovita samo ako se dade vrlo rano nakon nastupa ishemije. Tijekom posljednjih 20 godina različita neurozaštitna sredstva ispitivana su u moždanom udaru u mnogim kliničkim pokusima. Nedavno provedeni veliki klinički pokusi III. faze s nekoliko skupina neurozaštitnih sredstava (uglavnom antagonista NMDA receptora, čistača slobodnih radikala i blokatora kalcijevih kanala) nisu dokazali učinkovitost neurozaštite. Nakon prvotnog razočaranja djelatna se istraživanja nastavljaju, a na obzoru se naziru neki novi i uzbudljivi modeli neurozaštite.

Ključne riječi: *Cerebrovaskularni udar, lijekovi; Klinički pokus; Ishod liječenja; Neurozaštitna sredstva*