Acta neurol. belg., 2005, **105**, 144-148

Neuroprotection in acute ischemic stroke

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Abstract

Neuroprotection of patients with acute ischemic stroke should start at the scene and continue in the ambulance with the assessment and treatment of the airway, breathing, circulation, body temperature, and blood glucose. The key goal in eligible patients should be fast vessel recanalization with intravenous recombinant tissue-type plasminogen activator. Results from a meta-analysis suggest that systemic thrombolysis is effective when given within 4.5 hours after stroke onset. The time window extends to 6 hours for patients undergoing intravascular thrombolysis. Acute stroke patients should be admitted to stroke care units. A crucial component of neuroprotection is the prevention of secondary brain damage, which can be caused by hypoxemia, hypotension, hyperthermia and hyperglycemia. This can be achieved by avoiding complications, e.g. aspiration, and intensive control of oxygenation, hydration and blood pressure, body temperature, blood glucose, and cardiac monitoring. Neuroprotective agents are designed to try to salvage brain tissue within the penumbra. Thus far, despite promising preclinical studies, clinical trials with neuroprotective drugs in acute ischemic stroke have been disappointing. However, we have been able to identify many of the factors that were responsible for these failures, and better-designed clinical trials with neuroprotective drugs should look more promising. Mild induced hypothermia is another form of neuroprotective treatment that is currently being investigated in acute stroke.

Key words : Ischemic stroke ; stroke treatment ; thrombolysis ; secondary brain damage ; neuroprotection ; neuroprotective drugs.

Rationale for neuroprotection

Occlusion of a cerebral artery leads to reduced blood flow and availability of oxygen and glucose in the territory of the affected vascular bed. Neurons can withstand complete absence of blood flow for only minutes. Depending on the site and duration of the occlusion, the ischemic core is surrounded by a gradient of moderately to mildly reduced blood flow, the extent of which depends on the collateral supply from surrounding arteries (Astrup *et al.*, 1981 ; Hossmann, 1994). The moderately hypoperfused (cerebral blood flow 8-20 ml/100 g/min) nonfunctional, but still viable brain tissue surrounding the irreversibly damaged ischemic core is known as the penumbra. The mildly hypoperfused zone between the penumbra and the normally perfused brain tissue is a zone of oligemia where neuronal function is not affected.

In the prenumbra oxygen is insufficient to allow normal levels of oxidative metabolism. This curtails the production of ATP, which is the energy source of cellular ionic pumps. Failure of the sodium potassium pump results in massive uncontrolled neuronal depolarisation. This leads to the opening of voltage-sensitive calcium channels, mitochondrial dysfunction, an extracellular build-up of excitatory amino acids that overstimulate excitatory amino acid receptors, and persistently elevated intracellular calcium levels. An ensuing cascade of secondary biochemical changes will lead to necrosis or apoptosis of the penumbral cells (Obrenovitch, 1995 ; De Keyser *et al.*, 1999 ; Touzani *et al.*, 2001). However, there is a time window of several hours within penumbral cells may remain viable. By using positron emission tomography (PET) and magnetic resonance imaging (MRI) it has been shown that the penumbra in some humans can persist for 16-48 hours following stroke onset (Saunders *et al.*, 1995 ; Schwamm *et al.*, 1998 ; Heiss, 2000 ; Read *et al.*, 2000).

Neuroprotection by reperfusion

The goal of neuroprotection in acute ischemic stroke is to save neurons and glial cells in the hypoperfused area between the ischemic core and normally perfused brain tissue.

Intravenous thrombolysis with recombinant tissue plasminogen activator is currently the treatment of choice for acute stroke within 3 hours after symptom onset. Although treatment beyond the 3-hour time window has not been shown to be effective in any single trial, a meta-analysis suggest a somewhat less but still significant effect between 3

and 4.5 hours after stroke (Hacke *et al.*, 2004). Intra-arterial thrombolysis in well-selected patients is effective up to 6 hours after stroke (del Zoppo *et al.*, 1998). Endovascular reperfusion techniques are likely to be increasingly refined and may become a widely accepted therapy for acute ischemic stroke (Saver, 2001).

Prevention of secondary brain damage

Optimal medical care of stroke patients includes admission to stroke care units, a wide range of supportive measures to reduce the risk of complications and stabilize a number of acute physiological parameters that may worsen ischemia, hypoxia or the ischemic cascade. In the hypoperfused area, arteries are maximally dilated due to a loss of autoregulation. Mild to moderate reductions in blood pressure may result in a critical fall in cerebral blood flow and transform areas of oligemia in penumbra and areas of penumbra into infarction. Although not based on evidence, it is widely accepted that blood pressure reduction should only be accomplished cautiously when values above 220 mm Hg systolic and or 120 mm Hg diastolic are reached, or when other medical indications require lowering of blood pressure, such as aortic dissection or myocardial infarction (Sulter and De Keyser, 1999 ; Klijn and Hankey, 2003). Fluid and electrolyte management are also important. Many patients are dehydrated and intravenous fluid is indicated in most patients. Sustained low blood pressure (< 120/80 mm Hg) should be treated with plasma expanders, unless there are cardiac or renal contraindications, and when this fails with vasopressor drugs (Sulter and De Keyser, 1999 ; Klijn and Hankey, 2003).

Hypoxemia is poorly tolerated in areas of focal cerebral ischemia. Protection of the airway and maintenance of oxygenation are of paramount importance. Many patients with acute stroke have an abnormal respiration, which can lower arterial oxygen saturation. This should be corrected, on the basis of pulse oximetry, by the administration of oxygen through nasal prongs or a facial mask (Sulter *et al.*, 2000).

An elevated body temperature during the first days after a stroke is a predictor of poor outcome. Hyperthermia increases the metabolic demands in the penumbra and enhances the toxic biochemical cascade. As minor elevations in body temperature may exacerbate neuronal damage during brain ischemia (Reith *et al.*, 1996), it is important to maintain the patient in a normothermic state (De Keyser, 1998). However, this appears difficult to achieve with classical antipyretics such as acetylsalicylic acid and acetaminophen (Sulter *et al.*, 2004), and better therapies should be found to effectively reduce elevated body temperature in acute stroke. Infections should be treated aggressively.

Experimental evidence suggests that high levels of blood glucose may be detrimental for outcome after stroke. However, this may only apply for cortical infarctions and not for lacunar strokes (Sulter *et al.*, 1998 ; Bruno *et al.*, 1999). Treatment of elevated blood glucose levels is advised but there are no data from clinical trials to show that this improves neurologic recovery. When a protocol for normoglycemia is used in acute stroke patients, care should be taken to avoid overly aggressive therapy, especially in patients with poorly controlled diabetes mellitus, as this can result in hypoglycemia, fluid shifts and electrolyte abnormalities, all of which can be detrimental to the brain (Wass and Lanier, 1996).

Prevention of secondary brain damage by normalizing vital parameters and combating fever should already start at the scene or in the ambulance (De Keyser, 1998 ; Sulter and De Keyser, 1999). Evidence has been reported from a pilot study to suggest that admission of acute stroke patients to a stroke care unit with intensive monitoring of body temperature, oxygen saturation, blood pressure, and ECG can lead to improved outcomes (Sulter *et al.*, 2003). A further publication support the view that admission of acute stroke patients to a monitored stroke care unit may positively influence their outcome at discharge (Cavallini *et al.*, 2003).

Neuroprotective drugs

Various classes of neuroprotective drugs have been developed that have the potential to limit ischemic brain damage and improve the outcome for patients. These include sodium-channel or voltage-related calcium-channel blockers, potassium-channel openers, glutamate antagonists, magnesium sulphate, glycine antagonists, GABA-ergic compounds (such as clomethiazole), piracetam, citicholine, lubeluzole, growth factors (such as basic fibroblast growth factor), free radical scavengers (such as tirilazad), and anti-inflammatory compounds (such as enlimomab). Although preclinical and phase II studies for each of these compounds were promising, all phase III trials failed to convincingly demonstrate therapeutic benefit (De Keyser *et al.*, 1999).

The overall disappointing result of the phase III trials with neuroprotective drugs is multifactorial. First, failure to provide optimal stroke care to prevent secondary brain injury may override any beneficial effect of a neuroprotective agent. It is difficult to accept that stroke patients are still dying from aspiration pneumonia because no systematic attention is paid to the prompt detection of swallowing difficulties. In animal experiments, where neuroprotective agents show beneficial effects, physiological parameters, such as blood pressure, body temperature and oxygenation are strictly

controlled. We should do the same with stroke patients, and ideally patients should be admitted and treated in monitored stroke care units. It has been clearly shown in animal models that, for example, hyperthermia counteracts the beneficial effects of a neuroprotective drug (Gerriets *et al.*, 2003). Thus, optimal basic standard care in stroke care units is a prerequisite for the success of therapies with neuroprotective drug (Sulter and De Keyser, 1999). Clinical centers that are unable to provide optimal stroke care should not be allowed to participate in stroke trials with neuroprotective agents.

Second, many phase III trials were started under pressure of senior management of pharmaceutical companies without sufficient information about time window, optimal dosage, and length of therapy. In order to obtain this crucial information it is now possible to use proof-of-principle surrogate MRI endpoints. By using a combination of diffusion weighted and perfusion MRI it is possible to delineate the penumbra and follow the expansion of the ischemic core (Barber *et al.*, 2004). For some compounds, such as glutamate antagonists, clinically important side effects limit the possibility of achieving dose levels that have maximal neuroprotective effects in animals (Muir and Lees, 1995).

Third, the study population in many stroke trials was heterogeneous. Patients with cortical infarctions and lacunar infarction were lumped together, although they have a different pathophysiology and prognosis. Grey and white matter ischemia have different pathobiological mechanisms (Phan *et al.*, 2002). Thus, it is hardly surprising that no benefit is demonstrable when an operation designed to correct a particular pathophysiologic disturbance is performed in a group of patients in which many do not have that disturbance. For example, excitotoxic activation of neuronal N-methyl-D-aspartate (NMDA) receptors is one of the initial events that occur in grey matter ischemia, whereas in white matter strokes activation of AMPA/kainate receptors causes injury to glia (Phan *et al.*, 2002 ; Stys, 2004). Although white matter does not contain NMDA receptors, a number of trials with NMDA antagonists included patients with lacunar strokes. Planned subgroup analyses showed benefit of intravenous magnesium sulphate, given within 12 h of stroke onset, in lacunar stroke but not in cortical strokes (Muir *et al.*, 2004). We should abandon the idea that a pharmacological intervention in stroke should be applicable to all stroke types. Targeting patients with potential to benefit will increase the probability of a successful outcome.

Fourth, a beneficial effect of neuroprotective drugs may be masked because of adverse effects. Examples are the detrimental hemodynamic consequences of intravenous nimodipine (Ahmed *et al.*, 2000), and fever associated with the administration of enlimomab (2001).

Fifth, neuroprotective drugs must reach the penumbra in sufficient concentrations. In animal models of stroke, neuroprotective therapy is generally more effective if given to animals with reversible rather than permanent arterial occlusion. On the other hand, reperfusion can also lead to neuronal damage, so-called reperfusion injury. Experiments in animals suggest that selective neuronal necrosis may continue to occur in reperfused tissue (Li *et al.*, 1999). Neuroprotective drug treatment in combination with reperfusion should be a future goal in clinical research (Chen *et al.*, 2002). Neuroprotective agents mainly target a single pathway in the ischemic cascade leading to brain injury, and are most effective in animal models when administered before or very early (15-60 min) after the insult. Because longer inclusion times were used in the clinical trials with neuroprotective drugs, small treatment effects may have been missed with the classic outcome scales, such as the Barthel index or modified Rankin scale (Sulter *et al.*, 1999). Because animal studies suggest that therapies using a combination of different agents provide synergistic cerebroprotective effects and may extend the therapeutic window (Lyden and Lonzo, 1994 ; Auer, 1995 ; Barth *et al.*, 1996 ; Stuiver *et al.*, 1996 ; Onal *et al.*, 1997 ; Sobrado *et al.*, 2003 ; Culmsee *et al.*, 2004 ; Lapchak *et al.*, 2004), one should consider clinical trials with combinations of neuroprotective drugs.

Hypothermia

Hypothermia may reduce ischemic brain damage by preventing blood–brain-barrier disruption, lowering of the metabolic rate and counteracting the ischemic cascade in the penumbra (Olsen *et al.*, 2003). Hypothermia is neuroprotective in animal models of stroke, and is being investigated as an experimental therapy in acute stroke. Both surface cooling (cool-air fanning, cooling blankets or helmets) and endovascular cooling methods are possible options. Hypothermia might enhance the effects of neuroprotective drugs (Berger *et al.*, 2004 ; Nito *et al.*, 2004), and extend the therapeutic window for systemic thrombolysis or endovascular reperfusion techniques.

Conclusions

Reperfusion with thrombolysis is the neuroprotective intervention of choice, but is only feasible in a selected group of stroke patients. A major component of neuroprotection in acute ischemic stroke consists in preventing secondary brain damage. This should start at the scene and continue in stroke care units with monitoring and experienced professionals. Interventions to modify secondary injury factors need to be further improved. For example, we need better approaches than classical

antipyretics to reduce an elevated body temperature in stroke patients to a state of normothermia. More studies are necessary to determine how to manage hypertension and hypotension in acute stroke. The management of hyperglycemia in cortical stroke and lacunar stroke may require a different approach. Despite the disappointing results from controlled trials, the prospects for effective neuroprotective drug therapies to improve outcome following stroke still remain promising. Future interventions should focus on combinations of reperfusion and neuroprotective drugs. Whether hypothermia deserves a place in the treatment of patients with acute ischemic stroke remains to be seen.

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