Improving the outcome of acute stroke management

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Recent research into stroke mechanisms suggests that it may be possible to reduce mortality and improve functional outcome in stroke patients, provided clinicians act quickly and appropriately. In this article, standards for optimal stroke management with new therapeutic strategies aiming to restore cerebral blood flow and to protect brain neurons will be discussed.

The last 5 years have witnessed a remarkable evolution in strategies for treating acute stroke. Most strokes are now considered to be emergency cases. The site of the stroke can be specifically located, and following the introduction of new regimens designed to restore cerebral blood flow (CBF) using rapid thrombolysis or neuroprotective agents, we can reduce infarct size, preserve function and improve prognosis.

Acute circulatory impairment resulting from an obstructed cerebral artery causes a reduction in oxygen and glucose supply to the surrounding cerebral tissue. The extent of the ischaemic effects which follow depends on the degree of severity (i.e. critical 'threshold' perfusion <20 ml/100 g/minute, 20–30% of normal CBF) and the duration of the perfusion disturbance. The possible compensation provided by collateral pathways and the availability of haemodynamic and metabolic reserve capacities (i.e. an increase of blood volume within the cerebral autoregulation and an increase of oxygen extraction) are also contributory factors (Astrup et al, 1981; Symon et al, 1977; Garcia, 1992). The interaction between these factors determines whether transient dysfunction (so-called transient ischaemic attack; TIA) occurs, with or without structural tissue necrosis or a permanent infarction.

Ischaemic penumbra

The 'ischaemic penumbra' is a transient, narrow zone of tissue between the developing infarct and normal cerebral tissue. Originally, the term was used to describe dysfunctional cerebral tissue that was viable and, hence, recoverable. It was observed that, if rCBF rapidly returned to above-threshold values, electrical activity in this zone appeared to return to normal, implying that recovery of neurological function was also possible, even if the penumbra persisted for days or months in a chronic state. This concept has recently been modified as there is much evidence that the penumbra is a much shorter lived and heterogeneously distributed phenomenon (4–12 hours in primates) which results from a complex cascade of metabolic failure (Pulsinelli, 1992; Heiss and Graf, 1994; Phillis, 1994).

Whereas tissue in the core of ischaemia is destroyed after minutes of circulatory arrest (<10 ml/100 g/min), neurones and glial cells in the penumbra can survive a less severe reduction in the glucose/ATP reserve as long as no toxic substances initiate or increase cell destruction. Unfortunately, after the onset of ischaemia, anaerobic metabolism occurs and lactate, hydroxygen and nitroxygen ions accumulate in the tissue, which are toxic due to their characteristic release of free radicals. In addition, rapid imbalance of the acid–base relationship across the cell membrane triggers a whole series of biochemical events, including calcium, excitatory neurotransmitter and free radical release, ultimately leading to cell death.

GENERAL TREATMENT CONCEPTS

A basic concept which can be derived from the pathophysiological mechanisms is that stroke is an emergency, requiring a rapid diagnosis (by computed tomography (CT) or magnetic resonance imaging (MRI)), first in order to determine whether the event is caused by ischaemia or haemorrhage. This cannot be decided on clinical grounds alone and therefore makes brain imaging crucial.

Prognosis depends greatly on the early initiation of acute care management (*Table 1*). Patients should be admitted to hospital immedi-

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ately (ideally to specialized stroke care units) and monitored for at least 72 hours by a team of specialized clinicians, nurses and physiotherapists. Recent meta-analyses, which include several well-designed studies, have shown that stroke units reduce mortality and morbidity significantly (Ottenbacher and Jannell, 1993; Langhorne et al, 1993; Stroke Unit Trialists' Collaboration, 1995; Dennis and Langhorne, 1994). A recent consensus was that management on specialist units may be an appropriate and effective emergency intervention in acute stroke care (European Ad Hoc Consensus Group, 1996). This approach could prevent the deterioration of patients by 30–40% by avoiding many stroke-associated complications (*Table 2*).

In addition, attempts to prevent a secondary stroke may be initiated immediately, with early rehabilitation being an important goal. Furthermore, the physician must take into consideration the presence of associated disorders like cardiovascular disease (myocardial infarction, arrhythmia, hypertension) (Britton et al, 1980; Powers, 1993; Phillips, 1994; Phillips et al, 1995), infectious and metabolic disturbances (diabetes, hyperthermia) (Ameriso et al, 1991) or pulmonary conditions (oxygenation and respiration), particularly in patients with impaired consciousness, and avoid side-effects from inappropriate treatments (Qizilbash and Murphy, 1993; Rogvi-Hansen and Boysen, 1995).

Specific complications can occur days or even weeks after the onset of stroke, and can cause substantial morbidity and mortality (*Table 2*). Many of them are treatable and some are preventable; optimal management of the stroke patient from the time of his/her immediate admission into hospital is crucial if these are to be minimized or avoided.

Acute cerebral ischaemia may have an effect on cardiac function and vice versa. Knowledge of this interaction is not only important when early secondary preventive treatment is being considered, but also for identification and treatment of heart failure, dysrhythmia and coronary ischaemia during the acute stroke stage. Cardiac arrhythmias are a frequent finding and may cause stroke recurrences. Myocardial infarction and acute stroke can occur simultaneously (one potentially causing the other and vice versa) or one immediately after the onset of the other. New therapeutic strategies aim to restore CBF through thrombolysis and/or providing neuroprotection for those neurones in the penumbra region which may be salvageable.

THROMBOLYTIC THERAPY

While 90% of infarct-related arteries are occluded during the first few hours after stroke onset, spontaneous reperfusion occurs in up to 75% during the subsequent 24 hours (Fieschi et al, 1989). Results from clinical studies suggest that recombinant tissue plasminogen activator (rtPA) is useful to accelerate clot lysis and hence to improve stroke outcome if administered early (Hacke et al, 1995; National Institute of Neurological Disorders and Stroke (NINDS) Study Group, 1995).

The risks of thrombolytic treatment include secondary haemorrhage and haemorrhagic transformation, the risk of which increase depending on time delay of start of treatment and size of ischaemic tissue involved. Early start of treatment and a better selection of patients according to the individual stroke mechanisms active over time are

TABLE 1.
General recommendations for acute care management of the stroke patient

Recommended action	Comments	Further reading
Early placement of gastric tubes and venous catheters to reduce risk of aspiration, occasionally central venous pressure measurements	In patients with impaired consciousness and brainstem or large hemisphere infarcts	
Selective oxygenation by airway ventilatory assistance, blood gas determination, and pulse oximetry endotracheal tubes. Oxygen supplementation in hypoxic patients	Inadequate oxygenation may result from pulmonary infection, atelectasis or airways obstruction. Insufficient data about hyperbaric oxygen therapy	
Mild and controlled reduction of excessive hypertension (>220 mmHg/>120 mmHg)	Aggressive treatment is unnecessary and potentially harmful. Hypotension is also potentially dangerous	Powers (1993), Britton et al (1980), Phillips (1994)
Control of fever and infection with antibiotics and antipyretics. Hypothermia is probably not useful (or difficult to manage sufficiently)	Up to 40% of stroke patients have concurrent infections	Ameriso et al (1991)
Management of cerebral oedema: raise the head 20–30% in the supine position, raise blood pressure, provoke hyperventilation, use osmotic diuretics (e.g. glycerol) to avoid herniation and death	Hypoxia, hypercarbia and hyperthermia worsen oedema Furosemide (intravenous 40 mg once daily); intravenous mannitol (0.25–0.5 g/kg over 20 minutes up to 4x daily) may be useful. Surgical hemicraniectomy is not generally accepted but cerebellar craniectomy can save lives	Rogvi-Hansen and Boysen (1995)
Control of glucose, electrolyte and water metabolism	Corticosteroids not recommended	Qizilbash and Murphy (1993)

likely to improve the outcome, avoid unnecessary risks and hence cause a better risk–benefit ratio (Caplan et al, 1997; Schwartz et al, 1998).

The NINDS trial was organized and funded by the National Institute of Neurological Disorders and Stroke (NINDS Study Group, 1995). It included 624 patients randomized to receive either intravenous placebo or rtPA (0.9 mg/kg body weight to a maximum of 90 mg) given as a 10% bolus followed by an infusion lasting 60 minutes within 3 hours of onset of ischaemic stroke symptoms. Although there was no significant difference in early neurological recovery (within 24 hours), after 3 months patients given rtPA were about a third more likely to have no or minimal disability than the control subjects. Mortality was the same for both groups, but was surprisingly high in controls. Even though the NINDS study was well designed and conducted, and revealed a statistically positive result, the risk–benefit ratio was small and scepticism still exists with view to generalization (Caplan et al, 1997; Schwartz et al, 1998). Reasons for this could include the fact that there was only a 12% absolute increase in favourable outcome, but a 6% absolute increase in symptomatic brain haemorrhage, almost half of which were fatal; and the risk of symptomatic haemorrhage was higher than in any other similar trial, probably because the importance of early signs of infarction on the CT scan were underestimated.

The European Cooperative Acute Stroke Study (ECASS 1; Hacke et al, 1995) recruited 620 patients in a trial which was of similar design to the NINDS trial, except that treatment was initiated within 6 hours after onset of symptoms and the dose of rtPA was slightly higher (1.1 mg/kg body weight to a maximum of 100 mg). This trial failed to show either a reduced mortality or improvement in morbidity. By contrast, the mor-

TABLE 2.
Complications of acute ischaemic stroke

Type of complication	Specific complication	Comments	Further reading
General and systemic	Aspiration		
	Pneumonia		
	Hypoxia		
	Embolism (renal, pulmonary, peripheral vessels, artery-to-artery, venous iatrogenic)		
	Infection/fever		
	Thrombophlebitis, deep venous thrombosis		
	Endocrine changes		
	Decubitis, contractions		
Cardiovascular	Arrythmias (including atrial fibrillation)		
	Hypertensive dysregulation		
	Heart failure		
Neurological	Caused by increased intracranial pressure and cerebral oedema	Cerebellar craniectomy can avoid acute hydrocephalus and prevent brain herniation.	Schwab et al (1996) Plum (1996)
	Herniation	Drainage of CSF via an intraventricular catheter drastically reduces intracranial pressure and may be appropriate if hydrocephalus develops	
	Hydrocephalus		
	Brainstem compression		
	Death		
	Secondary haemorrhage (about 5% in computed tomography, 20–25% in magnetic resonance studies)	More common in patients with anticoagulants, cerebral embolism and thrombolytic treatment:	
		May remain asymptomatic	
		May cause severe oedema and brain herniation	
	Haemorrhage transformation		
	Seizures	Incidence is higher in haemorrhagic stroke (6–10%) than in ischaemic stroke (46%). Often occur within the first few days. Administer anticonvulsants	Pohlmann-Eden et al (1996, 1997)
	Depression	Incidence about 30%	
	Confusion	Incidence about 20%	

tality at 3 months was significantly higher in the treated group *vs* controls (22.4% *vs* 15.8%; $P<0.04$) and functional improvement was not seen at that time. In a difference from the NINDS trial, patients with early signs of infarction in more than one-third of the middle cerebral artery territory on CT should have been excluded, as it was suspected that these patients would be more likely to have a higher incidence of haemorrhagic complications. This suspicion was confirmed because, among those patients incorrectly included, haemorrhagic transformation with poor prognosis was a common finding (von Kummer and Forsting, 1993). As a consequence, analysis after exclusion of patients with incorrect CT interpretation and a few other invalid cases showed that there was a significantly better functional outcome in patients actively treated compared with those given placebo, irrespective of whether they were treated within 3 or 6 hours after onset of symptoms. Mortality rates did not differ significantly.

The ECASS II trial (Hacke et al, 1998) recruited 800 patients in a similar design to the ECASS trial, except that the rtPA dosage was reduced (0.9 mg/kg body weight) and CT criteria of early signs of infarction were strictly used as exclusion criteria — training in detecting these signs of infarction was successful, not only among neuroradiologists, but also among neurologists and internists. This resulted in the selection of patients with a reasonable collateral circulation and hence a favourable spontaneous prognosis, and so unusually small overall mortality rates (alteplase 11.1%, placebo 10.9%) resulted at day 90 when compared to ECASS (alteplase 22.4%, placebo 15.8%) or the NINDS trial (alteplase 17%, placebo 21%).

Although the study failed to prove superiority of alteplase, the trend towards efficacy was interpreted in the light of previous trials and a recent meta-analysis from the Cochrane Collaboration (personal communication, 1998) seems to support the positive risk–benefit ratio in a significantly greater proportion of independent and fully recovered rtPA-treated patients *vs* controls, however, a significant increase in unfavourable bleeding complications also became obvious.

Three recent large trials of streptokinase (ASK, Donnan et al, 1995; MAST-I, Multicenter Acute Stroke Trial, 1995; MAST-E, Hommel et al, 1994) administered within 4–6 hours after onset of stroke clearly showed negative results — all trials were discontinued prematurely because of a significant increase in mortality and brain haemorrhage.

The search to select patients who are most likely to show benefit from this type of therapy and to avoid treatment of those who either have a good prognosis or may only risk deterioration is still a major challenge (Caplan et al, 1997; Schwartz et al, 1998). The TOAST study (Gordon et al, 1993) has shown that in at least 40% of acute cases, even stroke experts fail to identify stroke subtypes on clinical criteria alone — new ultrasound and MR technologies rather than CT are promising tools to serve as surrogates (Hennerici, 1996; Russell, 1997).

ANTICOAGULANT AND ANTIPLATELET THERAPY

Other ways of re-establishing cerebral perfusion are through anticoagulation and platelet inhibition. Although generally considered to be limited to the purpose of secondary prevention, an early trial (Kay et al, 1995) suggested a beneficial suppression of leukocyte–endothelial interaction during the late (24–48 hours) phase of acute cerebral ischaemia — more recent studies, however, failed to confirm this observation (Hommel et al, 1998).

The large International Stroke Trial (IST) (1996), a multicentre study for the evaluation of safety and efficacy of low dose antithrombotic treatment in acute stroke failed to show any significant beneficial effect for administration of either aspirin (300 mg/daily) or subcutaneous heparin (12500 or 5000 U twice daily) *vs* placebo if initiated within 48 hours after onset of stroke. Only when combined with the results of another mega-trial (Chinese Acute Stroke Trial; Chen et al, 1997) aspirin produced a small benefit, with about 9 fewer deaths or non-fatal strokes per 1000 in the first few weeks.

Evidence for the benefit of high-dose heparin is still lacking, although it is often used in patients with severe cerebral artery stenosis (e.g. in the basilar or carotid arteries). Until more concrete evidence becomes available, current practice still includes full dose anticoagulation (i.e. activated partial thromboplastin time ratios 1.5–2.5) to patients at high risk of early stroke deterioration or recurrence (e.g. those suffering a stroke after recent myocardial infarction or those who are risk of secondary embolism, including patients who experienced non-valvular atrial fibrillation), although this is not consensus based (Adams et al, 1994; European Ad Hoc Consensus Group, 1996).

RHEOLOGICAL METHODS

Improvement of rCBF by rheological methods (e.g. haemodilution) has been used for a long time, but has never been shown to significantly reduce mortality or improve functional outcome. Fifteen randomized trials using isovolaemic or hypovolaemic regimens have failed to provide

evidence of benefit and one study using hypervolaemic regimens had to be prematurely discontinued for severe cardiac side-effects (Asplund, 1991). However, since reductions in haematocrit are known to increase rCBF by up to 33–35%, haemodilution may well be of benefit if administered early (<6 hours), which has never been looked at in a large enough study. As haemodilution is unlikely to cause significant deterioration, even in patients with cerebral haemorrhage, this concept may still be attractive for treating patients before their arrival at hospital.

NEUROPROTECTIVE THERAPY

Prompted by their reduction of stroke volume in animal models, a number of drugs have been tested for their ability to provide neuroprotection in the clinical setting. Neuroprotective agents are targeted at various levels along the metabolic ischaemic cascade.

Calcium antagonists

These selectively block presynaptic and postsynaptic calcium channels. Nimodipine has been studied most exclusively but, except for one small study, results have been disappointing (Mohr et al, 1994), although this trial was closest to demonstrate a potential benefit in patients with acute stroke receiving early treatmemt (American Nimodipine Study Group, 1992). Such a confirmative trial has unfortunately only recently been designed and is now underway (VENUS; Limburg et al, 1998).

Magnesium salts

These agents may possibly act as antagonists at the N-methyl-D-aspartate (NMDA) receptors (Diener et al, 1996). Although there is little experimental evidence of the neuroprotective activity of magnesium sulphate, this agent is currently investigated in the IMAGES (Intravenous Magnesium Efficacy in Stroke) trial. The lack of side-effects makes this study interesting.

Other drugs

Clinical trials with competitive and non-competitive glutamate antagonists (Minematsu et al, 1993; Fisher et al, 1994) and free radical scavengers (The RANTTAS Investigators, 1996) so far have failed either because of safety concerns or because of lack of efficacy.

Sodium channel blockers and potassium channel openers act on the electrical activity by hyperpolarization of the pre- and postsynaptic membrane to support glycosis and avoid cell destruction by preventing cell depolarization and so blocking action potential.

Lubeluzole is a benzothiazole derivative that protects against glutamate-induced neurotoxicity. The compound does not bind to the NMDA receptor complex but inhibits the glutamate-activated formation of nitric oxide that is toxic for neurones. Lubeluzole improved clinical outcome in stroke patients in a placebo-controlled trial in the USA (Grotta et al, 1997). A trial in Europe failed to show a benefit on clinical outcome and mortality — only in a post-hoc analysis a lower risk in mortality was found in a subgroup of mild to moderate stroke patients (Diener et al, 1996, 1998). A phase III trial which took the difference between both trials into account showed ne benefit from lubelozole (unpublished data, 1998.

CONCLUSIONS

Most clinical studies of drug therapies for acute stroke have had disappointing or confusing results so far. Thrombolytic agents may be useful for a few patients but they have significant side-effects. The development of new neuroprotectants, although negative overall if applied as a single treatment, still provides a hopeful future if administered in combination with vasoactive substances. As the aetiology of stroke is complex its management should be largely based on pathophysiological knowledge from well designed clinical trials. It is likely that the traditional methodology of designing clinical trials (i.e. either large trials with inclusion of heterogeneous stroke subtypes, for the sake of simple and less expensive technology *vs* small but expensive trials which focus on rare conditions) will not or too slowly solve the urgent need for really effective novel therapies. Therefore it is imperative that future studies are based on more stringent methodologies and eventually start using drug combinations. HM

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KEY POINTS

- Stroke is an emergency, similar to acute myocardial infarction, requiring an immediate admission to the hospital for full diagnostic and therapeutic evaluation.
- Skilled neurological examination and ongoing monitoring within 72 hours after onset of symptoms are essential, particularly to avoid complications and to prevent further deterioration.
- The patient should be treated by a specialized team on a 'stroke unit' with early rehabilitation (e.g. speech and swallowing therapies). Patients with impaired consciousness, or severe respiratory disturbances may need immediate intensive care unit assistance.
- General treatment concepts include cardiovascular and pulmonary aspects, control of blood pressure, metabolic disorders (e.g. diabetes and nutrition) and body temperature.
- Special treatment concepts address early clot lysis and neuroprotection (<3–6 hours after onset of symptoms).
- Corticosteroids and peripheral vasodilators should be avoided since they may increase intracranial pressure and oedema. Heparin should be administered in selected patients who have a high risk of deep thrombosis and secondary ischaemia in the presence of active sources of embolism.