

# The Past and Future of Neuroprotection in Cerebral Ischaemic Stroke

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## Key Words

Neuroprotection · Stroke · Ischaemia

## Abstract

Following the realization that cerebral tissue may survive for hours after an ischaemic insult, several agents with neuroprotective properties in small-animal models of cerebral ischaemia have been tested in patients with acute ischaemic stroke (AIS). Initial attempts at translating the positive effects of these agents from animal models to patients were unsuccessful, possibly as a result of poorly planned experiments in models of ischaemia, and/or clinical trials of AIS that were not optimized to show a positive effect. Newer neuroprotective agents that are believed to act later in the ischaemic cascade may offer a greater chance of success. However, before these agents can be introduced into clinical practice they must undergo assessment in rodent and large-animal models of AIS and, in particular, the dose-response relationship and the treatment time window should be defined. This should be followed by evaluation in carefully designed clinical trials of adequate power, involving subjects receiving an appropriate dose within an optimum time window following the onset of symptoms. There is hope that such careful strategies may guide continued progress in neuroprotective drug development.

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## Introduction

Stroke is a devastating condition, which annually affects 15 million people worldwide, and is the leading cause of adult disability in industrialized countries [1]. Three months following a stroke, 15–30% of stroke survivors are permanently disabled and 20% require institutional care [2]. In the Western world, over 70% of individuals experiencing a stroke are over 65 years of age. The most common cause of acute ischaemic stroke (AIS) is the sudden occlusion of a blood vessel either within the neck or inside the cranium, resulting in an almost immediate loss of oxygen and glucose to the cerebral tissue. Cerebral ischaemia triggers the pathological pathways of the ischaemic cascade that ultimately cause cell death in the ischaemic core within minutes of the onset of ischaemia [3]. The knowledge that cerebral tissue is very sensitive to ischaemia is the main reason for nihilism surrounding the development of remedies for acute stroke [4].

Management of AIS is a high-priority medical emergency [5, 6], and immediate action includes respiratory and cardiac care, as well as treatment of elevated intracranial pressure, blood pressure and establishing control of blood glucose. Some patients may also receive thrombolysis with the aim of re-establishing cerebral blood

flow. Intravenous recombinant tissue plasminogen activator (rt-PA) is currently the only drug therapy available for the thrombolytic treatment of AIS in the USA, Canada and Europe. However, use of rt-PA is greatly limited by the requirement of neuroimaging to exclude the possibility of intracranial haemorrhage and the restriction to use within 3 h of the onset of symptoms of AIS. As many as 95% of patients with AIS do not receive rt-PA [7] largely because the majority of patients do not present to hospital and undergo a CT scan within 3 h of stroke onset [8]. Additional reasons for patients not receiving rt-PA include the absence of a neurologist to administer rt-PA, and avoidable reasons such as delayed consultation [9, 10]. Even for patients who do receive treatment with rt-PA, less than 40% achieve systematic reperfusion or complete functional recovery [11], and 5% experience symptomatic haemorrhagic complications [12]. Although rt-PA has demonstrated efficacy in reducing death or dependency in terms of relative risk reduction (number needed to treat of 7), the disease impact number is considerably higher ( $n = 158$ ) because so few patients are suitable for treatment [13]. These factors highlight the urgent need for new therapeutic options for the treatment of AIS.

Neuroprotection may be an alternative strategy for the treatment of AIS and aims to limit the extent of irreversible damage that occurs to the neuronal cells surrounding the site of a stroke. Neuroprotectants disrupt the cellular, biochemical and metabolic processes that lead to brain injury, either during or after exposure to ischaemia, and encompass a wide and continually expanding array of pharmacological interventions [14]. An ideal addition to the stroke treatment armamentarium would be a well-tolerated neuroprotective agent that has the ability to reduce post-stroke disability. Several animal models for the evaluation of neuroprotectants for the treatment of AIS were developed during the late 1970s to 1990s in rodents, canines and primates. The mechanisms of cerebral ischaemia were studied in the settings of both transient global (mimicking cardiac arrest and severe systemic hypoxaemia) and focal ischaemia, and a variety of neuroprotectants were found to decrease the size of ischaemic lesions in these animal models [15].

It was envisaged that these agents would have similar 'neuroprotective' effects in acute stroke patients. Clinical trials involving neuroprotectants were first initiated during the 1980s and are still in progress [16]. However, the majority of these failed to extend any benefit of these agents from animal models to human patients. Despite the negative outcome of the trials, it is important to em-

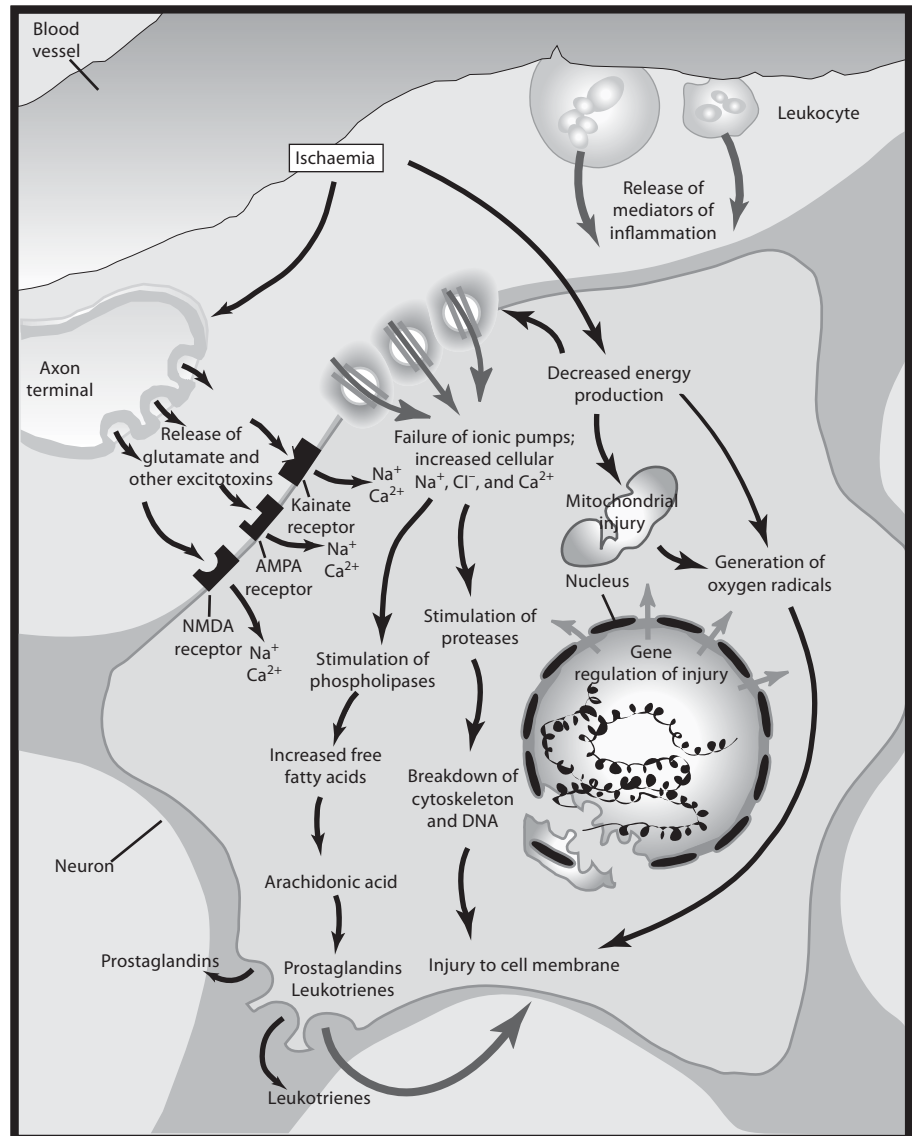
phasize that failure of these trials has led to an improvement in the methodology of stroke research.

This review will provide a brief overview of the current understanding of the pathophysiology of cerebral ischaemia and a discussion of what has been learnt from previous basic and clinical research into neuroprotection. This will be followed by an introduction to neuroprotection and why agents that have shown promise in animal models may have negative results in clinical trials. The development of NXY-059 from initial studies in focal transient and permanent ischaemia to the recently completed Stroke Acute Ischaemic NXY-059 Treatment (SAINT) I [17] and II [18] trials will be discussed. Finally, the future of neuroprotection in AIS considering the lessons learnt from previous trials will be explored.

### The Ischaemic Cascade

Within seconds to minutes after the loss of blood flow to a portion of the brain, the ischaemic cascade is rapidly initiated, which comprises a series of subsequent biochemical events that eventually lead to an area of neuronal death (infarct) (fig. 1). The ischaemic area consists of a core region of irreversibly damaged tissue surrounded by an area of potentially salvageable tissue known as the ischaemic penumbra. The penumbra has been extensively studied in recent years using pathological, electrophysiological, biochemical, radiological and non-invasive imaging techniques [19].

Animal models of AIS have been summarized previously [20], and preclinical research using these models reveals that the ultimate extent of damage in the central core region and in the penumbra can vary widely depending on the rapidity of blood flow reduction [21]. This damage is also linked to the extent of collateral circulation, and both brain temperature and blood glucose levels at the time of the ischaemic insult play an important role in how fast brain cells may die during an ischaemic insult [20]. In regions of the brain where blood flow decreases to below 10 ml per 100 g/min, there is a very rapid progression of neuronal cell death followed by death of other cell types in the cerebral matrix. In contrast, in regions where blood flow decreases to approximately 30 ml per 100 g/min, the ischaemic cascade progresses at a slower rate and neuronal cells may tolerate this level of reduced blood flow for several hours from the onset of injury with full recovery of function following restoration of blood flow [21].



**Fig. 1.** The ischaemic cascade. From Brott and Bogousslavsky [65], with kind permission. Copyright 2000 Massachusetts Medical Society. All rights reserved.

### Neuroprotection: Aims and Approaches

The aim of neuroprotection in AIS is to preserve viable brain cells in the ischaemic penumbra by interfering with the damaging events of the ischaemic cascade [3]. Limiting the area and impact of injury to neuronal cells in the ischaemic penumbra should improve neurological recovery and reduce disability from stroke [19]. In order to protect brain tissue within the penumbra, neuroprotective treatments, which are believed to act at one or multiple steps later in the ischaemic cascade, may have the greatest chance of success in clinical practice, although there would still be a need for rapid access to treatment within the therapeutic window.

A number of approaches have been taken to neuroprotection [22]. These include calcium channel blockade [23], calcium chelation [24], free-radical trapping [25], gamma-aminobutyric acid (GABA) and serotonin agonism [26, 27], and alpha-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-*D*-aspartate (NMDA) receptor antagonism [28, 29]. While a large number of neuroprotective agents have been shown to successfully reduce infarct size in animal models of focal and global ischaemia, neuroprotective compounds administered as monotherapy have failed to demonstrate efficacy for the treatment of AIS in phase III clinical trials in humans [15, 30, 31].

**Table 1.** Summary of failed trials of neuroprotective agents

Product	Mechanism	Outcome	Comments
Nimodipine	calcium channel blocker	mixed effects on outcome, not approved	blood pressure affects outcome [59]
Fosphenytoin	sodium channel blocker	phase III trial halted due to lack of efficacy	
BMS-204352	potassium channel opener	phase III trial failed, a second trial is being considered	
Selfotel	NMDA antagonist	preliminary results showed no efficacy in phase III trials	poorly tolerated with a potential neurotoxic effect in brain ischaemia [60]
Eliprodil	NMDA polyamine site blocker	phase III trials abandoned	hinders neuronal survival [61, 62]
Aptiganel	NMDA channel blocker	preliminary results showed no efficacy in phase III trials	may have detrimental effects in an undifferentiated population of stroke patients [62]
Gavestinel	glycine antagonist	preliminary results showed no efficacy in phase III trials	
Tirilazad	lipid peroxidation inhibitor	review of six trials showed that it worsened outcome	worked in reperfusion models only
Lubeluzole	ion channel and nitric oxide blocker	no efficacy in phase III trial	may be associated with a significant increase in heart conductance disorders [63]
Enlimomab	murine anti-ICAM-1 antibody	worsened outcome	immunogenicity [64]
UK-279,276	neutrophil inhibitory factor	unsuccessful phase II trials	worked in reperfusion models only
Trafermin	growth factor	phase II/III trials halted due to lack of efficacy	
Clomethiazole	GABA agonist	phase III trials halted due to lack of efficacy	administered up to 12 h following onset of stroke
Repinotan	5-HT <sub>1A</sub> receptor agonist	development halted due to disappointing results in phase IIb trial ( <a href="http://www.press.bayer.com">www.press.bayer.com</a> , accessed April 2005)	
ONO-2506	astrocyte-modulating agent	unfavourable interim analysis of phase II trial in the US	phase II/III study currently ongoing in Japan

Adapted with permission from Beresford et al. [22].  
ICAM-1 = Intercellular adhesion molecule.

### Reasons for Failure of Neuroprotectant Medications

A variety of general design ‘disconnects’ between pre-clinical studies and clinical trials have been suggested to account for the failure of many potential neuroprotectants during the development process (table 1) [22]. In particular, these relate to differences in the way com-

pounds are administered to animals and patients [15, 20, 32]. These factors can generally be divided into those that relate to a poor translational research process for bringing a neuroprotective agent from the preclinical to the clinical setting, and clinical factors that relate to outcome and sample size.

## Translational Research

There are a number of key factors that may contribute to the disappointing results seen in clinical trials, but perhaps the most important reason is that the majority of preclinical studies have been carried out using animal models that do not fully mimic the clinical situation. Although there are several rodent models of focal and global ischaemia, the majority of them have very little in common with the wide variety of mechanisms that lead to cerebral infarction in patients with acute stroke. There are substantial anatomical differences between the rodent brain and the human brain, particularly that the rodent brain has a higher grey-to-white matter ratio [33]. Primate models may be more useful as their brain structure more closely resembles the human brain. Clinical trials frequently enrol patients without specifying location of damage [15]. In animal models, physiological variables such as temperature and blood pressure are tightly regulated, and the severity of the ischaemic insult can be controlled. Also, young animals tend to be used, which is not representative of human stroke populations, which tend to be elderly, may suffer from multiple chronic diseases [32, 34] and take medications that have potentially negative effects on the final outcome. In addition, the presence of one or more previous cerebral infarctions may dampen reparative processes. Animal models utilizing aged animals, particularly primates, which are engineered to have other co-morbidities, such as diabetes and hypertension, will be more useful in mimicking human stroke and should be considered in future preclinical evaluation of neuroprotective agents.

Neuroprotective agents are generally more effective in animal models that incorporate reperfusion. This allows for better entry of the medication to the site of ischaemia. Compounds that are either only active in transient middle cerebral artery occlusion (MCAO) models or have to be administered at doses that are only effective in reperfusion models are unlikely to prove as effective in the clinical situation as monotherapy, especially in the presence of an arterial occlusion [20]. There are multiple pathways within the ischaemic cascade, yet the majority of neuroprotective agents only focus on single aspects of the cascade. These agents only slow the overall ischaemic cascade, as without tissue reperfusion, other aspects of the cascade proceed and cell death eventually occurs. Thus, neuroprotective agents should be thought of as an adjunct to reperfusion therapy, by either improving the efficacy or safety of reperfusion therapies. By slowing the ischaemic cascade and sustaining the penumbra tempo-

rarily, they may also allow for extension of the accepted therapeutic windows for reperfusion.

Another common problem that has been corrected in most recent studies relates to the timing of the medication to the arterial occlusion. While it is generally felt that the amount of penumbral tissue is greater early in stroke and declines with time, it has been difficult to determine exact time frames for penumbral survival, both in animals and in humans. This is due to the complexity of the penumbral area and collateral circulation, which varies greatly from individual to individual. These complexities have made it difficult to determine the best therapeutic window for preclinical and clinical trials. Early research utilized treatment that was begun either immediately before or within a short time of the insult. More recent animal research, however, attempts to extend the time window to 6 h or longer allowing for a more realistic comparison to the human situation. Similarly, in an attempt to increase enrolment into clinical trials there has been a tendency to use a long window to treatment from the onset of symptoms. In earlier studies this would be as long as 12 h or even longer. Recent trials are enforcing a more realistic window of less than 6 h from the time of onset of symptoms. This rigorous method led to a start of therapy mean time of less than 4.5 h in the SAINT I trial [17]. In addition, many animal studies involving neuroprotective agents have tested for the outcome of these agents very early after onset of MCA occlusion, which contrasts with the clinical trials where there is a much longer follow-up period (typically 3 months) for outcome. This makes evaluation of neuroprotective agents in clinical practice very different from the laboratory environment, and it may be that in preclinical studies the agents being tested are simply 'postponing' the eventual injury rather than truly offering permanent protection.

Clinical trials often fail to match the drug exposure (plasma levels) of animal studies that have maximal neuroprotective effects due to patients experiencing adverse events [20, 35]. Another potential difficulty for dosing studies is that higher concentrations of agents were found to be required for neuroprotective effects to be observed in a rat model of permanent ischaemia compared with transient ischaemia [20, 36].

There are also differences between preclinical and clinical studies in terms of outcome measures. In animal studies, the tools that measure the effects of neuroprotection are limited to assessing change in the volume of infarction by imaging or pathological tests, and a very basic evaluation of motor or cognitive skills [15, 16]. These simple scoring systems are very different from the assessments

that are required in human subjects. Most scores [for example, the modified Rankin Scale (mRS) or Barthel Index] measure more complex human behaviour including the ability to walk, take care of body needs and the ability to go back to activities that were possible prior to the AIS. Recognition of these factors by most researchers has led to improvement in the design of clinical trials in ischaemic stroke, with the aim of enrolling the largest number of patients in a time window that is less than 6 h from onset of symptoms. Animal studies have shown that if the stroke is too severe then the animal will die, but in contrast if the stroke is too mild no effects will be detected [37]. In addition, any initial differences in severity among treatment groups could have a greater effect on outcome than the treatment itself. To further try to optimize the effects of a new treatment, efforts are now being made to ensure that patients enrolled in clinical studies have moderate to moderately severe deficits on clinical assessment or, with sufficiently large trials, ensure that stratification for severity will adequately ensure groups to be well balanced. The most important variable to predict outcome is the National Institute of Health Stroke Scale (NIHSS), and the use of low and high cut-off points could be used to ensure standardized stroke severity across clinical trials [37].

### Clinical Factors

Although early reperfusion in ischaemic stroke has been associated with a 12% absolute improvement in independence in patients with an acute ischaemic stroke treated within 180 min of the event [38], this is unlikely to be the case for neuroprotective agents that aim to salvage penumbral tissue and which are administered at a later time point. Time is one of the most important determinants of success in any treatment strategy. In addition it is important to allow for a sufficient number of patients to participate in the study to achieve meaningful results. The sample size in clinical trials should ensure sufficient power to detect small, but clinically significant, differences in treatment effect [39].

There has been an improvement in the quality of data collected since all research staff who participate in clinical trials have to undergo training in trial procedures (NIHSS, Scandinavian Stroke Scale and Barthel Index), feedback on performance (Acute Stroke Therapy by Inhibition of Neutrophils and Potassium-Channel Opening Stroke Trial), and external monitoring [39]. In particular, there has been a recent trend to determine treatment effects in clinical trials with the mRS. This scale has

been validated and can be used to evaluate the effect of treatment even when a range of physicians with varied levels of neurological training conduct the test [40, 41].

In clinical trials, an appropriate selection of endpoints should be chosen and this is highlighted by the fact that the choice of outcome measures can influence the success or failure of a trial. To try to facilitate the analysis and comparison of results from future trials of neuroprotective agents in acute stroke, consistent and standardized outcomes of stroke should be used to assess a spectrum of stroke recovery [15, 42].

### Recommendations for Future Trials

Although the clinical trials involving neuroprotective agents have been negative, they have still provided useful information to try to devise optimal ways to test such agents in AIS. The Stroke Therapy Academic Industry Roundtable (STAIR) has produced guidelines for the pre-clinical and clinical evaluation of drugs for stroke treatment with the aim of reducing the number of failed trials in humans in the future (table 2) [5, 43, 44]. These recommend the modelling of clinical stroke through a greater use of functional tests in animal models and long-term outcome measures. Further recommendations have been made by Green et al. [20] to extend the guidelines for pre-clinical studies (table 2).

It is clear that there are differences between the rodent brain and that of humans and non-human primates, and there are associated difficulties with the scaling up of dosing regimens from rodents to humans. Therefore, it is considered appropriate to include an intermediate step involving large animals such as primates in the translation of neuroprotective agents from the preclinical to the clinical setting [43]. Recently there has been considerable interest in the use of surrogate markers to evaluate the drug effect in a smaller number of patients with AIS. The use of MRI technology to measure the volume of infarction as a marker of efficacy of therapy is increasingly being tested in a smaller number of stroke patients [45]. If such techniques are proven to be predictors of treatment effect, they may prove an excellent method to test drugs in a smaller patient population prior to more extensive and expensive trials. The technology is however expensive and not widely available in most hospitals. Alternatively, computed tomography utilizing perfusion techniques is rapidly advancing, and the widespread availability of this modality may make it a useful surrogate marker to consider in future research of neuroprotective agents.

**Table 2.** Essential criteria for optimal translation of preclinical to clinical trials

STAIR I [43]	STAIR II [44]	Green et al. [20]
Adequate dose-response studies with serum concentrations defining minimally and maximally effective doses	the likelihood of detecting clinical benefit is increased if enrolment is limited to patients with moderate baseline deficits	size of histological protection should be increased to 80%
Time window studies to confirm efficacy	patients should be enrolled as soon as possible after onset of stroke and within the time window observed in animal models	a compound should ideally attenuate damage in all brain areas including the subcortical region
Physiological monitoring	plasma levels should be attained, which have been shown to be neuroprotective in animal models	protection of the white matter should be examined since damage to this is a clear component of ischaemia in human brains
Randomized blinded studies that give reproducible effects (one independent laboratory)	both physician- and patient-rated scales should be used, which are appropriate to the expected clinical benefits and include a global outcome scale	potential treatment compounds may act on different biochemical components of the ischaemic cascade therefore it is vital that they are administered for a duration appropriate to the mechanism
Infarct volume and function measures, including short- and long-term assessment		require unequivocal evidence that a compound has efficacy as monotherapy before investigating as combination therapy
Efficacy evaluated in transient and permanent MCAO rat models		
Larger species such as primates should be used for novel, first-in-class agents		
Studies published in peer-reviewed journals		
With permission from Green et al. [20].		

## Development of NXY-059

### *Preclinical Development*

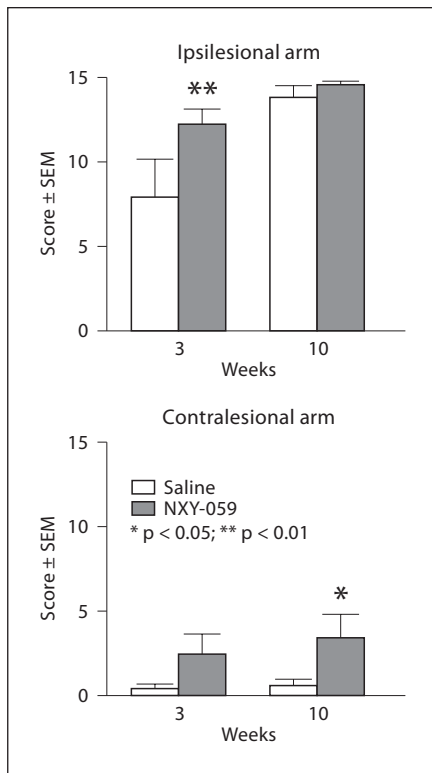
Of the numerous neuroprotective compounds tested, the novel free-radical trapping neuroprotectant NXY-059 was the first to meet all preclinical STAIR criteria and is the most advanced in development. Detailed reviews of the neuroprotective and free-radical trapping properties of NXY-059 in models of ischaemic and haemorrhagic stroke have recently been published [46, 47].

Preclinical studies have shown that NXY-059 reduces infarct size and preserves brain function in both transient [36, 48] and permanent [36, 49] MCAO models of focal ischaemia in the rat. The marmoset model has also been extensively used in testing behavioural and long-term effects of neuroprotection with NXY-059, and initial experiments tested the efficacy when the agent was offered 5 min after onset of focal ischaemia. There was robust protection in behavioural effects and the volume of infarction was significantly reduced in animals treated

with NXY-059 10 weeks following ischaemia [50]. However, it should be noted that marmosets are a non-gyrencephalic primate [50]. Subsequent studies evaluated the neuroprotective effects when NXY-059 was administered 4 h after the occlusion and using a drug exposure that was comparable to that known to be well tolerated by stroke patients [51]. NXY-059 produced improvements in motor paresis and spatial neglect (fig. 2, 3) up to 10 weeks after onset of ischaemia [47, 52], and was one of the first neuroprotectants where such detailed preclinical studies were completed prior to its clinical development. Of particular importance is the fact that the plasma concentration of NXY-059 was similar to that tested in patients in future clinical trials.

### *Clinical Development*

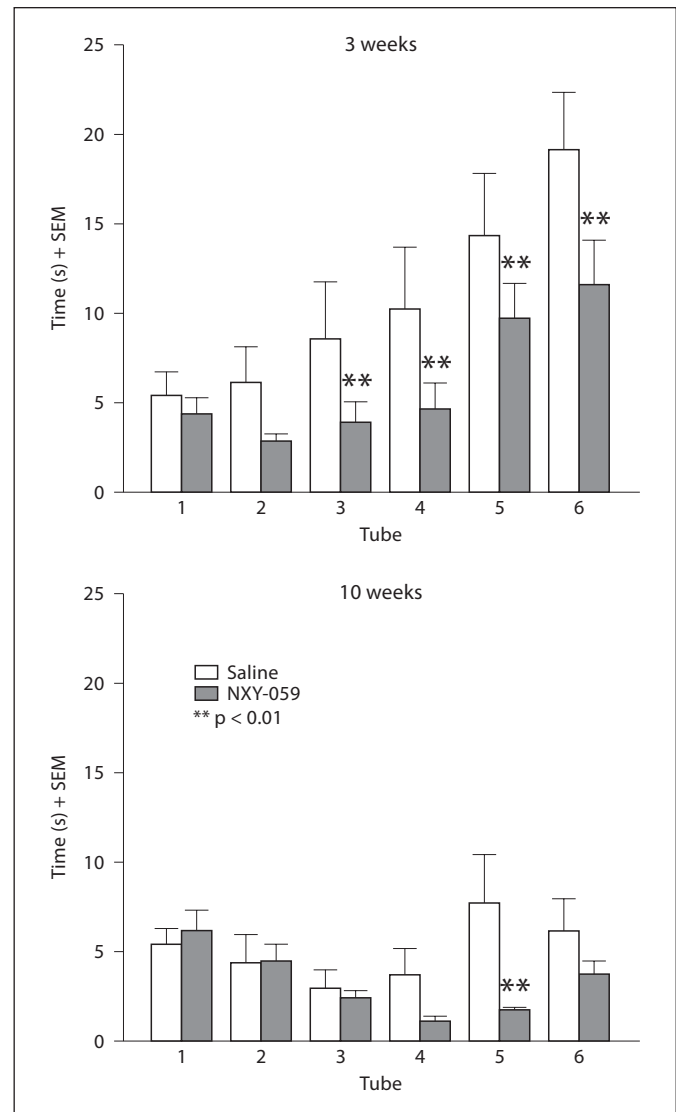
NXY-059 is well tolerated in stroke patients at doses that are neuroprotective in both transient and permanent MCAO models in animals [51, 53]. A population pharmacokinetic model for NXY-059 in acute stroke patients has



**Fig. 2.** Average score that saline-treated and NXY-059-treated monkeys achieved on the Valley staircase tests (allows examination of unilateral motor impairment and spatial neglect) with each arm 3 and 10 weeks after permanent middle cerebral artery occlusion. At 3 weeks, monkeys receiving NXY-059 were significantly better than those receiving saline at reaching with their unaffected right arm (ipsilesional) into neglected hemisphere. At 10 weeks, monkeys receiving NXY-059 were significantly better than those receiving saline at reaching with their affected left arm (contralesional) into right unneglected hemisphere [52]. With permission from Marshall et al. [52].

recently been developed [54]. This showed that the chosen dosing strategy for NXY-059 of an initial loading-dose infusion that is the same in all patients followed by a maintenance infusion individualized on creatinine clearance results in the early achievement of target plasma concentrations. This dosing strategy therefore satisfies the need for an easily adapted treatment regimen for AIS. However, despite evidence of excellent serum concentrations, concerns have arisen regarding how well NXY-059 crosses the blood-brain barrier [55].

NXY-059 has been evaluated in the SAINT clinical trial programme. This consisted of two phase III trials, SAINT I and SAINT II, whose trial designs are identical and consistent with the recommendations of the STAIR criteria (table 2) [44]. These carefully designed trials en-



**Fig. 3.** Time to find food reward hidden in one of six tubes positioned from the monkeys' far right (tube 1) to their far left (tube 6) (allows examination of spatial neglect). At 3 weeks, monkeys receiving NXY-059 were significantly better than those receiving saline at finding rewards hidden in the four leftmost tubes (tubes 3–6), and at 10 weeks this was still significant for tube 5 [52]. With permission from Marshall et al. [52].

rolled patients to NXY-059 or placebo up to 6 h after the onset of AIS. Unique features of the trial design include forced stratification to achieve an average time  $\leq 4$  h so that at least 50% of patients are enrolled early into the trial. In the SAINT I trial, 1,699 patients were included in the efficacy analysis and NXY-059 significantly improved the overall distribution of scores on the mRS as compared to placebo ( $p = 0.038$  as calculated by the Cochran-Man-

tel-Haenszel test). The mRS is a robust and simple test that is easy to understand by the patient and layperson [56]. The change in the distribution of the mRS at 90 days is more powerful and more relevant to testing neuroprotectants in the stroke population [57]. Results from SAINT I showed that NXY-059 significantly reduced global disability on the primary endpoint, mRS at 90 days compared with placebo ( $p = 0.038$ ) [17]. The benefits were seen irrespective of stroke severity, time to treatment and rt-PA use. NXY-059 was well tolerated and no safety issues were highlighted. An interesting feature that was evident in the post-hoc analysis of the SAINT I trial was the apparent decrease in the rate of asymptomatic and symptomatic haemorrhages in patients in whom NXY-059 was used in addition to rt-PA. The mechanism for this decrease in cerebral haemorrhage may potentially be related to the ability of NXY-059 to protect the cerebral vasculature from the effects of ischaemia.

The SAINT II study completed enrolment in mid 2006, and has been presented as an abstract at the 2007 International Stroke Conference [18]. It is the largest stroke treatment trial to date, with 3,306 patients randomized. Unfortunately, the study failed to meet its primary end-point or any of its secondary end-points. There was no improvement on mRS or any other parameters in the NXY-059-treated patients. The reduction in rt-PA-associated haemorrhage evident in the SAINT I study was also not evident in this much larger study. The manuscript is currently under review for publication. Astra-Zeneca reported that they were discontinuing the NXY-059 development programme. This is a major disappointment to the strategy of neuroprotection in the treatment of acute stroke.

### **Current Clinical Trials in Neuroprotection**

Failure of the NXY-059 programme has made the future of neuroprotection uncertain. The medication met all the STAIR criteria, yet the large SAINT II study failed to show the promise that we all so eagerly awaited.

What should the strategy be for future studies of neuroprotective agents? A few key concepts have become evident from previous studies. One is that neuroprotective agents are unlikely on their own to salvage the ischaemic penumbra. Decreased cerebral blood flow is the primary initiating event causing cerebral damage, and unless reperfusion occurs, the multiple pathways of the ischaemic cascade will eventually prevail. Thus, neuroprotective therapies should be thought more of as an adjunct to re-

perfusion therapies, producing either increased efficacy or increased safety of these agents. This may require that the multiple pathways of the ischaemic cascade be targeted by combining different neuroprotective agents acting on different points of the cascade, as targeting a single aspect of the cascade is unlikely to be efficacious. In addition, neuroprotective agents likely have to be administered very early on in the course of AIS to allow the agents the best chance of halting the ischaemic cascade.

A small number of clinical trials are ongoing with neuroprotective therapies utilizing varied strategies, including the use of albumin, magnesium and citicholine. The magnesium protocol (FAST-MAG) is a particularly exciting concept where the loading dose and the infusion is being initiated in the ambulance within minutes to hours after onset of symptoms [58]. If these studies were to show disappointing results, we may have to reconsider if indeed there is any role for neuroprotection in the treatment of acute ischaemic stroke.

### **Conclusions**

Although management of AIS is regarded as a high-priority medical emergency, patients have an unfavourable prognosis due to limited treatment options. Thrombolytic treatment with rt-PA is currently the only drug therapy available for AIS, but restrictions surrounding its administration highlight the unmet need for alternative strategies. Neuroprotection is one such strategy and aims to preserve viable cells in the ischaemic penumbra by interfering with the damaging events of the ischaemic cascade. By limiting the area and impact of injury to the neuronal cells in the ischaemic penumbra, neuroprotective agents could potentially improve recovery from stroke. However, poor translation from animal models to clinical trial design has accounted for the failure of many potential neuroprotectants and led to the development of STAIR criteria. The recent negative result of the SAINT II trial emphasizes the need to further refine our understanding of the ischaemic penumbra and the STAIR criteria, to try to improve the chances of successful translation and thus provide additional therapeutic options to ischaemic stroke patients.

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