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Clinical trials with neuroprotective drugs in acute ischaemic stroke: are we doing the right thing?

Jacques De Keyser, Geert Sulter and Paul G. Luiten

Ischaemic stroke is a leading cause of death and long-lasting disability. Several neuroprotective drugs have been developed that have the potential to limit ischaemic brain damage and improve outcome for patients. While promising results with these drugs have been achieved in animal stroke models, all Phase III trials conducted so far indicate that these drugs have failed to live up to their promise. Despite the limits of animal models, which cannot mimic the clinical situation, the disappointing results of neuroprotective trials might largely be due to methodological problems. Future trials with neuroprotective drugs should be performed in stroke (care) units, after sufficient information regarding therapeutic time window, dosage, duration of therapy and safety has been gathered from pilot studies, and a better selection of target patients has been made. Much of this information can now be obtained by techniques that visualize the penumbra, such as combined diffusion-weighted and perfusion MRI. Consideration should also be given to clinical trials with well-designed combinations of treatments.


A TARGET for acute intervention in ischaemic stroke is the penumbra, a zone of incomplete cerebral ischaemia, where neurons are functionally inactive but still viable. The development of the penumbra is a time-limited condition where cells will die in the ensuing hours to days, owing to a cascade of biochemical events, the so-called 'ischaemic cascade' (see Box 1).

Compounds that interfere with these biochemical steps have been demonstrated to be neuroprotective in preclinical models of stroke. A fraction of these have entered clinical development and some of those that survived early safety trials have been studied in randomized double-blind placebo-controlled efficacy trials (Phase III trials). Such trials require the courageous participation of many stroke patients, a 24-hours-a-day commitment of physicians from many centres and usually significant financial investment from a pharmaceutical company. The resources required to complete such a trial are estimated to be about 30–40 million US dollars. Despite these efforts, all Phase III trials have so far failed to demonstrate efficacy of neuroprotective agents (Table 1).

Na\(^+\)-channel blockers

The anticonvulsant phenytoin blocks voltage-dependent Na\(^+\) channels and reduces infarct size in both permanent and reperfusion models of focal brain ischaemia in rodents.\(^{24,25}\) Phosphonytoin is a prodrug of phenytoin that has been evaluated in a Phase III trial. Enrolment was halted after 462 patients had been included because no differences in primary or secondary endpoints were found in an interim analysis.\(^{13}\)

Ca\(^{2+}\)-channel blockers

One obvious treatment strategy for stroke involves the regulation of Ca\(^{2+}\) entry into the cell using inhibitors of voltage-sensitive Ca\(^{2+}\) channels. Nimodipine is an inhibitor of L-type Ca\(^{2+}\) channels, whereas flunarizine mainly acts as a T-type Ca\(^{2+}\)-channel blocker.\(^{26}\) Both these compounds can reduce infarct size when administered shortly after permanent and transient focal cerebral ischaemia.\(^{27}\) However, their potency is less than that of glutamate-receptor antagonists. Nimodipine has been studied most extensively and, in contrast to its beneficial effects in subarachnoid haemorrhage, it has produced unimpressive results in acute cerebral ischaemia. The intravenous administration even worsened outcome because of detrimental haemodynamic effects.\(^{28}\) A meta-analysis covering nine studies with oral nimodipine (120 mg/day) suggested a possible benefit when the drug was given within the first 12 h after onset of symptoms.\(^{29}\) The VENUS (very early nimodipine use in stroke) trial, which was conducted to confirm this hypothesis in a prospective manner, has been stopped because, in an interim analysis, no benefit of nimodipine became evident.\(^{30}\) Clinical development of flunarizine in stroke has been suspended after negative results of the FIST (flunarizine in stroke trial).\(^{31-33}\)

Glutamate inhibition or GABA stimulation

Inhibitors of glutamate receptors, particularly those that block NMDA receptors, can reduce infarction volume and neurological deficits in permanent and reperfusion models of focal cerebral ischaemia.\(^{34-38}\) The use of several NMDA-receptor antagonists was discontinued in Phase I and Phase II studies because of unacceptable adverse effects. The major problems with these compounds are psychomimetic effects (agitation, hallucinations, paranoia and delirium), sedation, catatonia and concerns about potential neurotoxicity.\(^{39}\) Only selegiline, a competitive antagonist at the NMDA binding site of the NMDA receptor, and apigatin, a non-competitive...
Neuroprotection drug trials have begun, but a Phase III trial was halted because sequential efficacy analysis did not demonstrate a significant difference from placebo. Clomethiazole is an anti-epileptic drug that causes neuronal hyperpolarization by enhancing the activity of GABA at GABA-A receptors. The rationale behind its use is that it could inhibit ischaemia-induced neuronal depolarizations and counteract the actions of glutamate. The drug protected against ischaemic cell damage in the penumbra of Cerebral Ischemia (Ter Horst, G.J. and Korf, J., eds), pp. 235–263, Humana Press.

References

in animal models of permanent and transient focal brain ischaemia. A large Phase III trial, involving 1,350 patients, produced negative results. A post hoc analysis suggested a beneficial effect in patients with severe stroke (total anterior circulation syndrome), which was the reason for initiating a new trial, the North American Clomethiazole Acute Stroke Study-I (CLASS-I). This study aims to include 1,200 patients with a total anterior circulation syndrome.

**TABLE 1. Major completed Phase III trials with neuroprotective drugs in acute ischaemic stroke**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Trial</th>
<th>Time window</th>
<th>Duration of treatment</th>
<th>Result</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosphenytoin</td>
<td>Na+-channel antagonist</td>
<td>4 h</td>
<td>3 days</td>
<td>No improvement of functional outcome at 3 months</td>
<td>2</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Ca2+-channel antagonist</td>
<td>TRUST</td>
<td>48 h</td>
<td>21 days</td>
<td>No improvement of neurological outcome at 6 months</td>
</tr>
<tr>
<td>American Nimodipine Study Group</td>
<td>48 h</td>
<td>21 days</td>
<td>No difference in mortality or neurological outcome at 21 days</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>German–Australian Stroke Trial</td>
<td>Nimodipine in Acute Ischemic Hemispheric Stroke</td>
<td>48 h</td>
<td>21 days</td>
<td>No improvement of neurological and functional outcome at 12 months</td>
<td>5</td>
</tr>
<tr>
<td>NEST</td>
<td>48 h</td>
<td>21 days</td>
<td>No improvement of neurological and functional outcome at 3 months</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>INVEST</td>
<td>24 h</td>
<td>21 days</td>
<td>Unfavourable outcome in the nimodipine groups</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>VENUS</td>
<td>6 h</td>
<td>10 days</td>
<td>No improvement of functional outcome at 3 months</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>Ca2+-channel antagonist</td>
<td>FIET</td>
<td>24 h</td>
<td>4 weeks</td>
<td>No improvement of neurological and functional outcome at 6 months</td>
</tr>
<tr>
<td>SeRotel (CNS 1102)</td>
<td>Competitive NMDA-receptor antagonist</td>
<td>ASSIST</td>
<td>6 h</td>
<td>bolus</td>
<td>Unfavourable risk-benefit ratio</td>
</tr>
<tr>
<td>Cerastat (CNS 1102)</td>
<td>Non-competitive NMDA-receptor antagonist</td>
<td>6 h</td>
<td>4 h</td>
<td>Unfavourable risk-benefit ratio</td>
<td>Unpublished</td>
</tr>
<tr>
<td>Elprodi</td>
<td>Polyamine-site antagonist at the NMDA receptor</td>
<td>CLASS</td>
<td>8 h</td>
<td>14 days</td>
<td>No improvement of functional outcome at 3 months</td>
</tr>
<tr>
<td>Clomethiazole</td>
<td>Enhances the effect of GABA at the GABA-receptor</td>
<td>12 h</td>
<td>24 h</td>
<td>No improvement of functional outcome at 3 months</td>
<td>11</td>
</tr>
<tr>
<td>Lubeluzole</td>
<td>NO-pathway modulator</td>
<td>LUB-INT-9</td>
<td>6 h</td>
<td>5 days</td>
<td>No reduction in mortality at 3 months</td>
</tr>
<tr>
<td>LUB-INT-5</td>
<td>6 h</td>
<td>5 days</td>
<td>No reduction in mortality at 3 months</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>LUB-INT-13</td>
<td>6-8 h</td>
<td>5 days</td>
<td>No improvement of functional outcome at 3 months</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Tirilazad</td>
<td>Free-radical scavenger</td>
<td>RANTASS</td>
<td>6 h</td>
<td>3 days</td>
<td>No improvement of functional outcome at 3 months</td>
</tr>
<tr>
<td>TESS</td>
<td>6 h</td>
<td>3 days</td>
<td>No improvement of functional outcome at 3 months</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Ebselen</td>
<td>Free-radical scavenger</td>
<td>Ebselen in Acute Stroke</td>
<td>48 h</td>
<td>2 weeks</td>
<td>No improvement of functional outcome at 3 months</td>
</tr>
<tr>
<td>Ganglioside GM1</td>
<td>Natural constituent of the cell membrane</td>
<td>EST</td>
<td>5 h</td>
<td>21 days</td>
<td>No improvement of neurological and functional outcome at 4 months</td>
</tr>
<tr>
<td>SASS</td>
<td>48 h</td>
<td>28 days</td>
<td>No improvement of survival, neurological and functional outcome at 3 months</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Citicholine</td>
<td>Natural constituent of the cell membrane</td>
<td>Citicholine in Acute Ischemic Stroke</td>
<td>24 h</td>
<td>6 weeks</td>
<td>No improvement of functional outcome at 3 months</td>
</tr>
<tr>
<td>Piracetam</td>
<td>Acts at the cell membrane and elevates cAMP levels</td>
<td>PASS</td>
<td>12 h</td>
<td>12 weeks</td>
<td>No improvement of neurological outcome at 4 weeks</td>
</tr>
<tr>
<td>Erlismab</td>
<td>Murine antibody to endothelial adhesion molecule 1</td>
<td>EAST</td>
<td>6 h</td>
<td>5 days</td>
<td>Unfavourable risk-benefit ratio</td>
</tr>
</tbody>
</table>

*aOnly trials enrolling more than 250 patients are listed.*

**NO-pathway inhibitors and free-radical scavengers**

The neuroprotective effects of lubeluzole can be explained, at least partially, by a downregulation of the NO synthase (NOS) pathway, which reduces NO-related neurotoxicity. In a small Phase II trial, a dose of 7.5 mg lubeluzole given within 6 h of the first symptoms, followed by 10 mg per day for five days, was associated with reduced mortality. A double-dose regimen, which yielded a plasma concentration equivalent to the levels...
associated with neuroprotection in rats, was associated with increased mortality23. Although this was probably caused by an imbalance of randomization that was unrelated to the drug, three large Phase III trials of lubeluzole, involving 3177 patients, were conducted with the 7.5 mg dose. All three trials failed to demonstrate a beneficial effect of lubeluzole on the primary outcome parameter24,25, and further clinical development has been abandoned (T. Wessel, pers. commun.).

Tirilazad is a non-glucocorticoid 21-aminosteroid lipid-peroxidation inhibitor that acts as a free-radical scavenger. In animals treated within 10–15 min of focal ischaemia this drug reduced infarct volume26. However, it did not improve the overall functional outcome in two large Phase III studies27,28. Because it was suggested that the lack of efficacy might be caused by the use of a dose that was too low (6 mg/kg/day for 3 days), higher doses were tested. These trials were stopped prematurely because of safety problems and further clinical study of tirilazad in ischaemic stroke has been suspended29.

The seleno–organic compound, ebselen, which has antioxidant activity through a glutathione-peroxidase-like action, was studied in Japan. This drug appeared to improve outcome at one month, but not at three months after the start of treatment30. Further efficacy studies with this compound might be justified.

Drugs that mainly act at the cell membrane

In preclinical studies, the ganglioside, GM1, conferred protection against ischaemic and excitotoxic insults31. However, two major Phase III trials produced negative results32,33. Because of concerns regarding a possible association with the development of Guillain–Barré syndrome34, GM1-ganglioside product licences have been suspended.

After a number of small inconclusive clinical trials with citicholine (cytidine-5-diphosphocholine or CDP-choline), a multicentre dose-finding study in the USA suggested a better functional outcome in stroke patients receiving 300 mg citicholine per day given orally for six weeks35. However, this result could not be reproduced in a pivotal trial involving 394 patients36.

Piracetam is another compound that mainly acts on cell membranes of both neurones and blood cells37. A placebo-controlled multi-centre study in Europe failed to show an improved outcome at three months38. Post hoc analysis suggested an improvement in neurologica! outcome in a subgroup of patients treated with piracetam within 6 h of the onset of stroke. A new Phase III trial, PASS-2, has recently been initiated in order to confirm these results.

Anti-inflammatory agents

Within hours, endothelial adhesion molecule 1 (ICAM1) levels are increased in the zone of focal cerebral ischaemia, which allows an influx of white cells into the ischaemic brain area. Cytokines released from the invaded white cells contribute to brain-tissue damage. ICAM1 antibodies reduced infarct volume in rats, only when the model included reperfusion, but not with permanent middle-artery occlusion39. Enlimomab, a murine monoclonal antibody against ICAM1, has been studied in a Phase III trial. Yet again, the results in the clinical situation did not fulfill the expectations generated in the laboratory40. There was even a trend for early neurological deterioration in patients receiving active treatment. A probable explanation is that the murine antigens present in the enlimomab preparation themselves provoked an inflammatory response that cancelled out any beneficial effects by raising body temperature.

Why were the trials negative?

Animal models

Because all the Phase III stroke trials with neuroprotective drugs failed to live up to their promise, one could argue that the animal models that have been used to test these substances have no predictive value. Focal ischaemia models can be broadly categorized into two types: permanent and reversible41. In patients, both types of focal ischaemia can occur42,43. Both forms of insult can produce a potentially salvageable penumbra. In the transient-occlusion model, reperfusion injury also adds to the rating, for most of the drugs mentioned above, neuroprotective activity has been demonstrated in different types of animal models, including permanent and reperfusion models of middle-cerebral-artery occlusion. However, animal models will never mimic the clinical situation and, therefore, these models should be regarded merely as a method to screen whether a particular compound has the ability to rescue neurones in the ischaemic penumbra when administered after the insult. Although these animal models are indispensable when investigating these compounds, experiments designed to measure functional outcome three months after the ischaemic insult in a larger number of animals, as required for Phase III trials in patients, cannot be justified because of ethical, practical and economic reasons. Because of concerns regarding a possible association with the development of Guillain–Barré syndrome, GM1-ganglioside product licences have been suspended.

Heterogeneity of the stroke population

Animal data are usually collected in healthy laboratory rats of the same age, in which a standardized amount of focal cerebral ischaemia is induced by a reproducible intervention. In contrast, aetiology, location and severity of ischaemic stroke in patients is very heterogeneous. Some patients have a large cortical infarction, whereas others have a lacunar infarction with a completely different prognosis44. Some patients have a poor collateral circulation and, hence, a smaller penumbra or no penumbra at all44,45. Some patients show spontaneous reperfusion in the early stages after stroke and tend to have a better clinical outcome than those without reperfusion46. It is also hardly surprising that no benefit can be demonstrated when an operation designed to correct a particular pathophysiological disturbance is performed in a group of patients, many of whom do not have that disturbance. For example, one in four patients enrolled in a trial with clopidogrel had lacunar white-matter infarctions47, where there are no neuronal GABA receptors to be stimulated.

Other factors that could exaggerate brain damage

In animal studies, other variables might affect infarct size and outcome, such as blood pressure, body temperature and oxygenation, which are all carefully controlled during the experiments. It is known that a reduction in blood pressure, hypoglycaemia, hypoxia and increased body temperature can all aggravate cerebral
More attention should be paid to properly conducted trials that have accumulated over the past decade. It appears that the overall disappointing results of clinical trials using tirilazad and NMDA-receptor antagonists are probably due to protocol and dosage problems. Other side-effects clearly overide the putative beneficial effect of a neuroprotective drug. Examples are the detrimental haemodynamic consequences of intravenous nimodipine and an inflammatory reaction associated with the administration of enlimomab. Normally, such problems should be detected in properly conducted Phase II trials, but there is often so much pressure from senior management in pharmaceutical companies to rush for registration that well-conducted Phase II trials are often neglected.

In some trials, suboptimal doses are used because too much emphasis is placed on safety aspects, although side-effects might be acceptable or properly controlled in an acute care setting. This could account for the failure of labezulox in the penumbra, where a possible misinterpretation of limited Phase II data and concerns about CTC-interval prolongation on the ECG led to the decision to use a dose regimen that was probably below its neuroprotective threshold. Another problem is that side-effects can limit the duration of treatment with a neuroprotective drug. Although it is not known exactly how long neuroprotective therapies should last, fear of side-effects, such as sedation, can shorten the duration of treatment to levels that are insufficient for protecting the penumbra. For example, clomethiazole was administered for 24 h after the onset of stroke, although it had been demonstrated that excitatory-amino-acid levels in the ischaemic area could remain grossly elevated for at least six days after the onset of stroke.

Therapeutic time window

In many animal studies some drugs are effective only if given before or very early (between 15 min and 2 h) after the insult. Typical examples are nimodipine, tirilazad and NMDA-receptor antagonists. Other compounds, such as nimodipine, are still effective in reducing ischaemic brain damage when given up to 6 h after the onset of ischaemia. Although the penumbra in humans can exist for a longer period than in rodents, the animal experiments indicate that treatment should be started within the first few hours in order to have any chance of success. Neuroprotective drugs should be administered as long as the ischaemic cascade occurs, which can be as long as six days after the insult of enzymes that are released during the course of ischaemic brain damage, such as neutrone-specific enolase and S100 (Ref. 58). No compromise should be made with respect to the dosage or duration of treatment below the therapeutic threshold in order to avoid side-effects.

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Future prospects

In view of the fact that it is not possible to translate from the animal model to the clinical situation, it appears that the disappointing results of clinical trials that have accumulated over the past decade are probably due to protocol and dosage problems. More attention should be paid to properly conducted Phase II trials in order to obtain sufficient information regarding therapeutic time window, dosage, duration of therapy and safety. In small sample sizes of patients, information might be obtained by invoking surrogate parameters. These include imaging techniques that visualize a potentially salvageable penumbra, such as combined diffusion weighted and perfusion MRI, or the determination of serum levels of enzymes that are released during the course of ischaemic brain damage, such as neutrone-specific enolase and S100 (Ref. 58). No compromise should be made with respect to the dosage or duration of treatment below the therapeutic threshold in order to avoid side-effects.

Optimal standard care is a prerequisite for the success of a stroke trial, and, therefore, pivotal trials with neuroprotective drugs should be performed in stroke (care) units. In addition, we should abandon the unrealistic idea that a pharmacological intervention in stroke should be applicable to all stroke types. Neuroprotective trials should be conducted in patients who are likely to have the pathophysiological disturbance that the compound was designed to treat. By using combined diffusion-weighted and perfusion MRI we should be able to identify more rationally appropriate candidates for neuroprotective therapies.

Combination therapy

All neuroprotective agents studied so far target a specific pathway of the ischaemic cascade. It is evident that the administration of either an NMDA-receptor antagonist or a voltage-dependent Ca2+-channel blocker will not be able to control excessive neuronal Ca2+ accumulation completely. Although these compounds can reduce infarct size in animal models, we should not expect that any single drug that interferes with a specific event in the ischaemic cascade will have a large clinical impact. In fact, the effects might not be measurable with the crude clinical outcome measures that are currently used, such as the Modified Rankin Scale, the Glasgow Outcome Scale or the Barthel Index. Instead of continuing with single drug trials, it might be more rewarding to explore treatments using a combination of reperfusion with neuroprotection and a cocktail of carefully selected neuroprotective drugs.

Animal studies have shown that combination therapies have synergistic effects. Examples are the combination of labezulox and diazpsrin-croslinked haemoglobin, thrombolyis with recombinant tissue plasminogen activator (r-tPA) and a glutamate-receptor antagonist and the combination of a glutamate-receptor antagonist (MK801) with basic fibroblast growth factor.

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PERSPECTIVES ON DISEASE

Cholinergic correlates of consciousness: from mind to molecules

In their recent article, Elaine Perry and her co-authors illustrate elegantly that ACh is one of the important neurotransmitters that regulates consciousness. One line of reasoning is that many anesthetics appear to operate through an ACh-mediated mechanism. These authors provide us with a concise and useful summary of ACh-mediated mechanisms of anesthesia. However, no certain conclusion can be drawn about the underlying mechanism of consciousness on the basis of the literature that deals only with the ACh. So does a possible answer lie outside the literature on ACh? Stuart Hameroff has proposed a mechanism for anesthesia that is independent of a particular neurotransmitter. His proposal is that anesthetic gas molecules inhibit quantum states produced by endogenous Van der Waals dispersion forces, which occur

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