

Pharmacologic Neuroprotection: The Search Continues

Hilary P. Grocott, MD

University of Manitoba, Winnipeg, Canada

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Abstract: Dozens of drugs have been studied in an attempt to mitigate the adverse cerebral consequences of cardiac surgery. The targets for these drugs have focused on pathways identified through the cascade of events that occurs once cerebral ischemia is initiated. In addition, inflammatory targets specific to cardiopulmonary bypass have also been addressed. Although no drugs are yet approved as specific neuroprotective agents, trials con-

tinue of increasingly unique targets, with fewer unwanted side effects and acting through novel mechanisms of action. This review summarizes the past, present, and future of pharmacologic neuroprotection for cardiac surgery. **Keywords:** cardiac surgery, cardiopulmonary bypass, brain, neuroprotection, pharmacology. *JECT. 2007;39:296–301*

INTRODUCTION

Cerebral complications continue to be a well-recognized source of morbidity and mortality after cardiac surgery (1). Although the early decades of cardiac surgery were largely focused on improving myocardial outcome and its effect on overall patient survival, neurologic injury was clearly recognized. The study of cardiac surgery-related cerebral injury has since followed a logical time-course establishing a stepwise path toward the goal of neuroprotection. Initial descriptive studies focused on the incidence of, and risk factors for, perioperative neurologic injury. In addition to studies of the cerebral physiologic effects of cardiopulmonary bypass (CPB), multiple technologic advancements in the CPB apparatus were also identified, thus forming the early basis for non-pharmacologic methods to prevent neurologic injury. Early efforts to identify pharmacologic neuroprotectants (e.g., barbiturates) developed based on the understanding of the apparent importance of metabolic suppression to protect the ischemic neuron. In addition to the improvements in CPB technology, knowledge of the molecular workings of the brain has improved significantly, revealing potential pharmacologic neuroprotective targets.

The understanding of the pathophysiology of cerebral injury continues to evolve. The oversimplified concept that depletion of high energy phosphates and the destruction of brain tissue that rapidly follows ischemia has largely been replaced with more complex temporal, topo-

graphic, and biochemical considerations. Imaging techniques have elaborated on the spatial gradations of residual blood flow in the downstream territory of an occluded cerebral vessel. This ischemic “penumbra,” where blood flow is critically reduced but still sufficient to prevent immediate cell death, has formed the basis for drug therapy targeted to rescue this vulnerable yet salvageable tissue. There is a marked difference in the temporal association between the ischemic insult and eventual cell death, thus defining the “therapeutic window” during which intervention may attenuate infarct size.

An ischemic cascade is triggered by reductions in cerebral blood flow (CBF), either globally or regionally, when the demands of cerebral metabolism ($CMRO_2$) are no longer met (2). This depletion in cerebral energy stores leads to membrane ionic pump failure and a consequent series of injurious events mediated through the influx of sodium, the opening of voltage-dependent calcium gates, a release of stored intracellular calcium, and overall membrane depolarization. Membrane depolarization results in the release of excitatory amino acids (glutamate, aspartate) with subsequent dramatic increases in intracellular calcium. This increase in cytoplasmic calcium propagates the cascade through the activation of a number of calcium-dependent enzymes, including endonucleases, nitric oxide synthase, various proteases, protein kinases, and phospholipase. Without intervention, these enzymes eventually lead to neuronal death.

Although some of these ischemic cascade pathways are potentially reversible if reperfusion is quickly re-established, reperfusion itself may initiate a number of other destructive pathways. The re-establishment of oxy-

Author for correspondence: Hilary P. Grocott, hgrocott@sbg.h.mb.ca

gen delivery provides substrate for the production of free radicals. Reperfusion can initiate a number of other damaging extracellular events including blood-brain barrier breakdown, endothelial swelling, and localized thrombosis that together may culminate in microvascular occlusion and further ischemia. Each ischemic cascade pathway represents a specific target for neuroprotection and has formed the basis for the initiation of pharmacologic neuroprotective strategies, both in non-surgical, as well as cardiac surgery, settings.

There are currently no pharmacologic therapies approved by the regulatory agencies for the prevention or treatment of cardiac surgery-associated cerebral injury. Numerous studies of specific pharmacologic agents have been undertaken in cardiac surgery studies, and it continues to be an active area of research. The most relevant cardiac surgery pharmacologic neuroprotection strategies, past and present, will be reviewed below. In addition, future trials, either being planned or underway, will also be reviewed.

PHARMACOLOGIC NEUROPROTECTIVE DRUGS

Anesthetic agents have long been thought to possess neuroprotective properties and were among the first compounds studied for neuroprotection in cardiac surgery. Indeed, the barbiturate, thiopental, was one of the first agents studied for this purpose during cardiac surgery. In a study by Nussmeier et al. (3), thiopental was administered (until EEG burst suppression) before aortic cannulation and continued until separation from CPB. Postoperative neurologic complications on postoperative day 10 were significantly reduced in the thiopental group vs. controls. Based on the encouraging results of this trial, high-dose thiopental was frequently used for valvular and other open ventricular procedures. The proposed mechanism for this neuroprotective effect related to the salutary effects of barbiturates on cerebral metabolism. This mechanism, along with considerable experimental data reporting the beneficial effects of the barbiturates (4), made it a logical choice for cardiac surgery. However, further studies of the use of thiopental were not quite as positive. A study by Pascoe et al. (5) and one by Zaidan et al. (6) failed to support a beneficial effect of thiopental on neurologic outcome after cardiac surgery. These negative trials coupled with the side effects of prolonged sedation tempered the optimism for barbiturates. Retrospectively examining the initial study of Nussmeier et al., the beneficial effects of thiopental, although not shown in longer-term follow-up, may not have been related to a direct neuroprotective effect per se, but because of an indirect effect on reducing emboli-containing CBF. The well-known cerebral vasoconstricting effects of thiopental (coupling CBF with a barbiturate-induced reduction in

CMRO₂) may have resulted in a reduction in embolic load to the brain during CPB, and as a result, a beneficial effect on neurologic outcome. Furthermore, it has subsequently been experimentally shown that isoelectricity per se is not necessary to confer neuroprotective benefit from barbiturates (7). The evaluation of burst suppressive doses of thiopental have not been performed in this setting.

Propofol has similar effects on CMRO₂ and CBF as thiopental. In addition, it has also been shown to possess some antioxidant and calcium-channel antagonist properties (8). This, along with supportive data from the experimental cerebral ischemia studies (9–11), led to propofol being evaluated as a neuroprotectant during cardiac surgery. A prospective randomized clinical trial by Roach et al. (12) determined whether propofol-induced EEG burst suppression would reduce the incidence or severity of cerebral injury during valvular surgery. However, in 109 of 215 patients randomized to receive burst-suppressive doses of propofol, there was no beneficial effect on cognitive outcome at 2 months. These authors concluded that propofol provided no neuroprotection during valvular cardiac surgery. One caveat is that studies in non-valve cardiac surgery have not assessed the effects of propofol on the brain, but one can speculate that the results would be no different.

Clomethiazole, an antagonist at the γ -aminobutyric acid (GABA) receptor, has recently been evaluated in coronary artery bypass grafting (CABG) surgery. The rationale to this study was that GABA has repeatedly been shown to be an important neuroprotective target in focal and global experimental ischemia (13,14). However, in a relatively large well-designed and conducted study, it failed to have any effect on preventing neurocognitive dysfunction after cardiac surgery (15).

The adenosine-regulating agent, acadesine, was studied in the early 1990s with the expressed purpose of improving myocardial outcome. However, evaluations for stroke (as a secondary outcome) were also performed (16). Compared to placebo, both high- and low-dose infusions of acadesine resulted in a lower stroke rate ($p = 0.016$) (17,18). Despite this positive (albeit indirect) clinical data and supportive experimental data, no further clinical neuroprotection indication for acadesine has been pursued (19). There are a number of other adenosine-like agents that in pre-clinical experimental settings have provided neuroprotection.

Aprotinin is a non-specific serine protease inhibitor that was first used for the treatment of pancreatitis. Its current indication in cardiac surgery is for the prevention of blood loss and transfusion. In several large multi-center trials of aprotinin for primary or redo CABG and valvular surgery designed to evaluate its blood loss and transfusion reducing effects, high-dose aprotinin patients suffered fewer strokes compared with placebo patients ($p = .032$)

(20,21). In a similar fashion, Frumento et al. (22) retrospectively examined patients at high risk for stroke (because of the presence of significant aortic atheroma); those who received aprotinin had a significantly lower stroke rate. In a recent small ($n = 36$) study examining the effects of aprotinin on cognitive deficits after CABG surgery, the incidence of cognitive loss was reduced in the aprotinin group (58% aprotinin vs. 94% placebo; $p = .01$) (23). However, the high incidence in the placebo group, coupled with the small size of the study and other methodologic concerns, limits the applicability of these results to broader populations (24). Furthermore, animal studies in cerebral ischemia models have failed to show any direct benefit on either functional or neurohistologic outcome after cerebral ischemia (25).

There has been considerable discussion and study as to the potential mechanism for any aprotinin-derived neuroprotection. Initial enthusiasm focused on its anti-inflammatory effects potentially preventing some of the adverse inflammatory sequelae of cerebral ischemia. However, any direct neuroprotective effect may have been mediated through an indirect effect in modulating cerebral emboli. Brooker et al. (26) identified the cardiomy suction of mediastinal shed blood as a major source of cerebral emboli during CPB. One could extrapolate that, if a drug reduces the amount of particulate-containing blood returning from the operative field to the cardiomy reservoir (by decreasing overall blood loss), cerebral emboli (and the resulting neurologic consequences) might also be decreased.

More recently, additional doubt as to any direct neuroprotective effects of aprotinin has been tabled in a controversial publication by Mangano et al. (27). Contrary to the previous data that suggested, albeit very weakly, that aprotinin may have some neuroprotective effects, this particular study outlined a significant increase (181%) in the stroke rate after cardiac surgery. Although the observational nature of this study and the propensity analysis used to control for the high risk of the patients receiving aprotinin did not delve into the mechanism for this potential side effect, it has been suggested that any potential neurologic risk is likely related to prothrombotic effects. However, the multiple modes of action of this non-specific serine protease inhibitor make it difficult to confidently explain these results based on one solitary mechanism. In summary, the data suggesting that aprotinin had any neuroprotection were somewhat indirect and weak; however, the data suggesting that it is neurologically detrimental are similarly just as weak. The true effects of aprotinin on the brain remain incompletely understood and would benefit greatly from prospective study.

The influence of calcium plays a central role in propagating cerebral ischemic injury. For this reason, as well as a shown beneficial effect of the calcium channel blocker

nimodipine in subarachnoid hemorrhage and experimental cerebral ischemia, a randomized double-blind placebo, single center trial to assess the effect on nimodipine on neurologic, neuro-ophthalmologic, and neuropsychologic outcomes after valvular surgery was performed (28–30). However, the trial was stopped before completion of enrollment because of safety concerns related to an increased bleeding and death rate in the nimodipine group. In addition, there was also no difference in neuropsychologic deficits between the placebo or nimodipine groups at this interim review. As a result, the effect of this drug, or similar calcium trial blockers, will likely never be fully elucidated in CPB.

The monosialoganglioside, GM1-ganglioside, has also been studied as a potential neuroprotectant during cardiac surgery (31). In addition to the potential beneficial effects of this class of compound on preserving neuronal membranes, there are also some data to suggest that it has a potential beneficial effect on reducing excitatory amino acid transmission (32). In a preliminary (but underpowered) cardiac surgery study, no beneficial effect was shown. This trial highlights one of the biggest difficulties in this investigative field—the interpretation of negative but underpowered studies.

The *N*-methyl-D-aspartate (NMDA) receptor is known to play a central role in the ischemic cascade (2). Although human stroke trials have been limited by variable psychomimetic side effects, there is considerable experimental data identifying NMDA receptor antagonists as robust neuroprotective agents. It has also been postulated to play a potential role in CPB-associated cerebral injury (33). In a well-designed and executed study by Arrowsmith et al. (33), the effects of remacemide, given orally for 4 days before CABG, was assessed by administering a neurocognitive battery performed at 1 week before and 8 weeks after CABG. A deficit was defined as a decrease in 1 SD in 2 or more of the 12 tests within the neurocognitive battery. In addition, the patients were evaluated for their learning ability by subtracting the postoperative neurocognitive score from the preoperative score (thus formulating a Z score). Although there was no difference between groups with respect to the binary outcome of cognitive deficit ($p = .6$), examination of a continuous measure of learning ability showed a beneficial cognitive effect in the remacemide patients ($p = .028$). Despite these apparently beneficial results, this drug was never pursued for this indication. This was in part because of the length of time that it took to perform this single center trial, the initial non-beneficial preliminary results, and a prolonged period of data analysis and review for publication. It did, however, highlight the potential use of this class of drugs for this indication and, as a result, ongoing studies examining other NMDA receptor antagonists continue (34–36).

A second NMDA receptor antagonist that has been evaluated for neuroprotection during cardiac surgery is dextromethorphan. Dextromethorphan, known for its anti-tussive activity, has been shown to have some non-specific NMDA antagonism properties. A small ($n = 12$) pilot study in pediatric cardiac surgery examined dextromethorphan using both EEG and magnetic resonance imaging endpoints to determine a difference between treatment groups. However, no difference was found, most likely because of the small size of the study (37). There have been no other studies examining NMDA receptor antagonism in the setting of pediatric cardiac surgery.

Ketamine, a frequently used anesthetic that is also an NMDA receptor antagonist, was evaluated for its neuroprotective effects in a small ($n = 106$) study in cardiac surgery patients (38). The incidence of neurocognitive dysfunction 10 weeks after surgery trended toward being lower in the ketamine group (20% ketamine vs. 25% controls; $p = .54$), but because the study was underpowered, it was not a significant change. There are no other published trials evaluating ketamine for neuroprotection in this setting.

Lidocaine has both properties as a sodium channel-blocking agent and potential anti-inflammatory effects. It has been studied as a neuroprotectant in cardiac surgery in several studies. In a study of 55 patients undergoing valvular surgery, a lidocaine infusion (1 mg/min) was started pre-induction and maintained for 48 hours after CABG surgery (39). Neurocognitive testing was performed pre-operatively and then 8 days and 2 and 6 months post-operatively. Compared with placebo, neurocognitive outcome 8 days after the surgery was significantly better in the lidocaine group ($p = .025$). However, a much larger, and more definitive, double blind randomized trial in cardiac surgery failed to replicate the finding. Interestingly, not only did lidocaine not confer any benefit, but in diabetic patients, it actually worsened neurocognitive outcome. Currently, lidocaine cannot be recommended as a clinical neuroprotective agent in cardiac surgery (40).

β -blocker use in patients with cardiac disease has predominantly been directed towards the prevention of adverse myocardial events. However, in a retrospective study ($n = \sim 3000$) of neurologic outcomes after cardiac surgery, β -blocker use was associated with an improvement in composite neurologic outcome (stroke and encephalopathy) (41). Patients receiving β -blocker therapy had a significantly lower incidence of neurologic deficit vs. those not receiving β -blockers. Although the reasons for this potential benefit were not clear, there are several potential reasons why they may be efficacious. For example, β -blockers have been shown to modulate both cerebrovascular tone and CPB-related inflammatory events. Support for the potential neuroprotective effects from β -

blockers has similarly been shown in a study of carvedilol, a mixed adrenergic antagonist effect also possessing anti-oxidant and anti-apoptotic effects (42).

Reactive oxygen species (ROS) production is a well-described pathophysiologic mechanism of ischemic reperfusion injury. When combined with the whole body inflammatory response associated with CPB (and its own associated generation of ROS), the field of antioxidant therapies for neuroprotection after cardiac surgery has emerged. Superoxide dismutase (SOD) is involved in the catabolism of free radicals, and SOD mimetics have had beneficial results in the setting of experimental ischemia. Pegorgotein, a monomethoxy polyethylene glycol covalently linked to SOD, has experimentally been shown to be protective against reperfusion-mediated cardiac and neuronal injury (43). A clinical trial was carried out to examine whether it would be associated with a reduced number of neurocognitive deficits after cardiac surgery (44). However, in a study of 67 patients undergoing CABG surgery ($n = 22-23$ in each of three groups: placebo, 200 IU/kg pegorgotein, or 5000 IU/kg pegorgotein), no difference in neurocognitive outcome was found.

Complement activation is central to the inflammatory response initiated with CPB (45). In a small ($n = 18$) study using a simple assessment of cognitive function, patients receiving an inhibitor to C5 (h5G1.1-scFv; pexelizumab) showed fewer visuospatial deficits at hospital discharge (46). Additional large (phase III) trials of this compound to more adequately delineate any potential longer-term neuroprotective effects from this drug in this setting have been performed. Mathew et al. (46) studied pexelizumab in a 914 patient study aimed at evaluating its effect on both myocardial outcome and mortality. The secondary endpoint of neurocognitive outcome showed that pexelizumab, although having no effect on overall global measures of cognitive outcome, seemed to have a specific benefit on the visuospatial domain.

Platelet activating factor (PAF) antagonists have been shown to have neuroprotective effects in various experimental models of cerebral ischemia (47). PAF modulates post-ischemic injury through the release of cerebral cellular lipids and free fatty acids that consequently lead to cellular injury and cerebral edema (48). In a study of 150 cardiac surgery patients by Taggart (49), patients receiving either placebo or one of two different doses of Lexiphanth showed no protective effects on neurocognitive outcome 3 months after cardiac surgery. However, this study was again underpowered, which is a recurring and troublesome feature of many studies in this area.

Because of their ability to reduce the inflammatory response, corticosteroids have long been considered as potential cerebroprotective agents. Inflammation is considered an important factor in propagating ischemia-mediated brain injury (50,51). With the exception of spinal

cord injury (52), steroids have never been shown to possess any significant clinical neuroprotective properties. Indeed, in a prior CABG trial, they actually had an adverse effect on postoperative pulmonary function (53). Furthermore, the administration of steroids has been shown to worsen cerebral outcome in a recent large ($n = 10,000$), although non-cardiac, surgical trial. The CRASH trial showed an increased relative risk of death (1.18; 95% confidence interval, 1.09–1.27; $p = .0001$) in those receiving high-dose steroids within 8 hours of head injury (54,55). Part of their lack of effect may be because of the hyperglycemia that generally follows their administration. Hyperglycemia, in animal models and several human studies of cerebral injury, has been associated with worsened neurologic outcome (56,57). Hyperglycemia has also been shown to increase the incidence of cognitive deficits after CPB (58). The administration of steroids with the intent of conferring some degree of neuroprotection during cardiac surgery cannot be recommended.

FUTURE NEUROPROTECTIVE DRUG TRIALS

There are several drugs undergoing active study as neuroprotective agents in the setting of cardiac surgery. Most of these drugs use neurocognitive dysfunction, or mild cognitive impairment, as a primary endpoint.

Dexanabinol is one such potential neuroprotective compound that is a synthetic non-competitive NMDA receptor antagonist. It also possesses some tumor necrosis factor (TNF)- α antagonist properties. Its neuroprotective potential has been evaluated extensively experimentally in the setting of various models of cerebral ischemia (59,60). It is currently being evaluated in early phase clinical trials in CABG for the prevention of neurocognitive dysfunction. In addition to the dexanabinol trial, other peptides are also under study. One of these, AL-208 is an eight amino acid activity-dependent neurotrophic factor that is secreted by allele cells in response to stimulation by vasoactive intestinal protein. In addition to anti-apoptotic activity, it has also been shown to promote neurite outgrowth and stabilize microtubules. It is currently underway in a phase II trial in CABG surgery.

Another growth factor-related peptide, glypromate (glycine-proline-glutamate), is an insulin-like growth factor 1 and has completed a small phase II trial ($n = 30$). Furthermore, a small phase I CABG trial ($n = 20$) was undertaken of the energy substrate-providing ketone body drug, KTX-0101 (sodium α -hydroxybutyrate), but the results have not been reported. Several other proprietary compounds are also undergoing evaluation and have yet to be reported.

In summary, despite decades of work, and the studies of dozens of drugs, the prospect of having a robust pharmacologic neuroprotective agent does not yet seem promis-

ing. However, with a better understanding of the etiology and mechanisms of neurologic injury, studies will continue to be undertaken. Clearly, when it comes to neuroprotection, the search continues, but the answers have thus far remained elusive.

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