Review Article

Brain protection: physiological and pharmacological considerations. Part II: The pharmacology of brain protection

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Neuroprotective agents may exert their effect by reducing cerebral oxygen demand ($CMRO_2$), increasing cerebral oxygen delivery, or by altering ongoing pathological processes. Barbiturates provide neuroprotection by reducing the $CMRO_2$ necessary for synaptic transmission while leaving the component necessary for cellular metabolism intact. Isoflurane may exert a neuroprotective effect by a similar mechanism but its efficacy is likely less than that of barbiturates due to adverse effects on cerebral blood flow. Lidocaine reduces $CMRO_2$ by affecting both cellular metabolic processes and synaptic transmission and thus resembles hypothermia in its mechanism of action. Benzodiazepines reduce $CMRO_2$ by reducing synaptic transmission and their use as neuroprotectants produces less haemodynamic compromise than barbiturates. The mechanism of protection by calcium entry blocking agents appears to be due to improved blood flow as opposed to altering abnormal Ca^{++} fluxes. In contrast, agents such as ketamine and MK-801 may prevent abnormal Ca^{++} fluxes through their competitive interaction with N-methyl-D-aspartate receptors. Phenytoin prevents K^+-mediated ischaemic events from progressing. Agents worthy of further investigation include corticosteroids, free radical scavengers, prostaglandin inhibitors and iron chelators.

Key words

ANAESTHETICS, INTRAVENOUS: ketamine, thiopentone;
ANAESTHETICS, LOCAL: lidocaine;
ANAESTHETICS, VOLATILE: isoflurane;
ANTICONVULSANTS: phenytoin;
BRAIN: blood flow, injury, ischaemia, metabolism, oxygenation, protection;
HORMONES: corticosteroids;
HYPNOTICS: barbiturates, benzodiazepines;
PHARMACOLOGY: calcium channel blockers, flunarizine, lidoflazine, nimodipine;
RECEPTORS: NMDA.

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On peut protéger le cerveau soit en diminuant ses besoins ($CMRO_2$) ou en améliorant son apport en oxygène, soit en modifiant le processus pathologique sous-jacent. Les barbituriques exercent leur action protectrice en diminuant les besoins en oxygène nécessaires à la transmission synaptique tout en laissant intacte la composante requise par le métabolisme cellulaire. L'effet protecteur de l'isoflurane tient du même mécanisme mais son efficacité est sans doute limitée par un certain degré de vasodilatation cérébrale. A l'instar de l'hypothermie, la lidocaïne diminue le $CMRO_2$ associé au métabolisme cellulaire et à la transmission synaptique. Les benzodiazépines quant à elles, n'agissent que sur cette dernière, mais elles préservent mieux l'équilibre hémodynamique que les barbituriques lorsque employées pour fin de protection cérébrale. Les bloqueurs des canaux calciques semblent exercer leur effet protecteur plus par une amélioration du flot sanguin cérébral que par une normalisation du transport du calcium. Par contre, la kétamine et le MK-801 semblent pouvoir empêcher les flux calciques anormaux en agissant sur les récepteurs de N-méthyl-D-aspartate. La phénytoïne empêche la redistribution du K^+ induite par l'ischémie, limitant ainsi les dommages. Le potentiel de protection cérébrale offert par les corticostéroïdes, les inhibiteurs des prostaglandines et les chélateurs du fer ou des radicaux libres mérite d'être étudié plus à fond.

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Conclusions

Brain protection may be defined as the "prevention or amelioration of neuronal damage evidenced by abnormalities in cerebral metabolism, histopathology or neurologic function occurring after a hypoxic or an ischaemic event."[1] It includes therapy directed at both the prevention of ischaemic cerebral pathology and the resuscitation of tissue that has already sustained ischaemic damage.

Agents used as brain protectants can exert their protective effects at three basic levels:[1-3]

1 Reduction in oxygen demand.
2 Increase in oxygen delivery.
3 Arresting deleterious pathological intracellular processes.

However, these categories are not absolute as any one agent may have efficacy on more than one process.

Barbiturates

The primary CNS protective mechanism of the barbiturates is attributed to their ability to decrease the cerebral metabolic rate, thus improving the ratio of oxygen (O_2) supply to O_2 demand. More specifically, it has been suggested that these agents selectively reduce the energy expenditure required for synaptic transmission, while maintaining the energy required for basic cellular functions.[4-6] A redistribution of cerebral blood flow (CBF) to ischaemic tissues[7,8] and a reduction in intracranial pressure (ICP)[9] may contribute secondarily to the metabolic effect.

Other possible mechanisms that may contribute to the protective effect of barbiturates during central nervous system ischaemia are given in Table I.

Focal ischaemia

Barbiturate therapy has been suggested to be particularly protective in cases of focal ischaemia.[4,7,17-22] In this type of ischaemia, even though oxygen supply is reduced, synaptic activity is still occurring. These tissues benefit from the barbiturates' selective reduction in synaptic activity thus enabling the oxygen that is delivered to be allocated solely to general cellular maintenance needs. This improves the oxygen supply to oxygen demand ratio by reducing oxygen demand. This ratio may be secondarily improved as a result of a barbiturate induced redistribution of CBF to ischaemic areas.[1]

ANIMAL MODELS OF FOCAL ISCHAEMIA

Barbiturate protection from neurological injury has been studied in various animal models of incomplete ischaemia.[7,8,17-21] Some of these studies have suggested improved neurological outcome as a result of barbiturate therapy.[17-21]

Michenfelder *et al.* found that pentobarbital improved neurological outcome in Java and squirrel monkeys with a middle cerebral artery occlusion, but could not demonstrate a beneficial effect in gerbils, dogs, and cats.[17,18]

Hoff *et al.* permanently occluded the middle cerebral artery (MCA) of one hemisphere in the baboon brain while the animals were anaesthetized with either pentobarbitone or halothane (control) prior to occlusion.[20] Histopathological examination of the two groups revealed

TABLE I Mechanisms by which barbiturates may exert a cerebral protectant effect[1,4-16]

Reduction in synaptic transmission
Redistribution of cerebral blood flow
Suppression of seizures
Reduction in cerebral oedema
Scavenging of free radicals
Alteration of fatty acid metabolism
Suppression of hyperactivity induced by catecholamines
Reduction in cerebrospinal fluid (CSF) secretion
Membrane stabilisation
Anaesthesia, deafferentation, and immobilisation

the ability of the barbiturates to reduce the extent of infarction that followed the focal ischaemic event.[20] The dose at which the barbiturates were found to deliver the greatest protective effect (90 $mg \cdot kg^{-1}$), however, was also commonly accompanied by severe side effects including cardiac arrhythmias, systemic hypotension and prolonged ventilatory insufficiency.[20] Such doses in humans may be expected to produce marked cardiovascular and respiratory effects.[20] It was suggested that more tolerable doses of barbiturates (e.g., 60 $mg \cdot kg^{-1}$) might be used in conjunction with other therapeutic measures, such as hyperventilation and hypothermia, to provide a comparable level of cerebral protection in man, but without the adverse effects.[20]

Corkill *et al.* were able to demonstrate in a canine model of experimental stroke that post-occlusion intramuscular administration of barbiturate (pentobarbitone) is effective in attenuating cerebral infarction.[21] In addition, they observed a dose-dependency of protection over the range of 10–40 $mg \cdot kg^{-1}$ with significant reduction in infarct size occurring by 15–20 $mg \cdot kg^{-1}$ levels.[21] However, it should be noted that none of the dogs was given any respiratory or cardiovascular support and at higher doses (50 and 80 $mg \cdot kg^{-1}$) the respiratory depressant effects of the barbiturates prevailed and death of the dogs ensued.[21]

Application of the results of animal studies to humans has been hampered by the conflicting results which have been reported. Animal studies are often executed utilizing different species and with different methodologies. The applicability of these animal studies to one another and to man is difficult as the pathophysiology of human cerebral injury may not be duplicated by the animal model.

HUMAN MODEL OF FOCAL ISCHAEMIA

Unlike most clinical circumstances for which barbiturate therapy for brain resuscitation has been studied (e.g., cardiac arrest, stroke, head trauma – see later), one can predict that, during cardiac surgery requiring cardiopulmonary bypass, an episode of cerebral ischaemia may occur. During cardiac surgery, barbiturates are employed as preventative rather than resuscitative therapy. Cardiac surgery serves as a useful model within which to study the CNS protective effects of drugs in man.

However, it was not until the work by Nussmeier and associates that a human study demonstrated any significant cerebral protection by a barbiturate.[23] Based on previous work in cardiac surgical patients,[24] they identified a subset of patients at highest risk for developing neuropsychiatric dysfunction during cardiac surgery, i.e., those patients undergoing surgery requiring an open ventricle, e.g., valvular replacement. They administered thiopentone to maintain an isoelectric EEG throughout the period during which incomplete ischaemia might occur. They identified the period most likely to be associated with embolization of air or particulate matter – aortic cannulation and weaning from cardiopulmonary bypass – and administered thiopentone to include these periods.

They emphasized that emboli leading to focal neurological damage are the primary cause of neuropsychiatric complications during cardiopulmonary bypass, an observation supported by other researchers.[25]

The overall incidence of persistent neuropsychiatric complications in the thiopentone treated group was significantly reduced when compared with the control group of patients (thiopentone – none; control – 7.5 per cent). Both the thiopentone and control groups initially developed neuropsychiatric dysfunction at the same rate, although dysfunction was only temporary in the thiopentone group. This suggested that barbiturate therapy reduced the incidence of neuropsychiatric dysfunction, not by reducing the frequency of embolization but rather by modifying the clinical expression of these emboli through a reduction in the infarct size.[23] This hypothesis has been supported by both canine and primate models of focal cerebral ischaemia.[17–21]

In their study, Nussmeier *et al.* were able to confirm some observations made in previous studies and also to provide some observations of their own. There was a positive relationship between the incidence of neuropsychiatric complications and the duration of cardiopulmonary bypass,[26] and a lack of any relationship between these complications and low perfusion pressure.[27,28] There was a higher incidence of neurological complications following aortic valve replacement, particularly in those patients with calcification of the valve.[23] This led the authors to suggest that emboli arising from the field of operation were the major cause of neuropsychiatric complications.

Although thiopentone therapy was successful in improving the neurological outcome following cardiopulmonary bypass and open ventricle surgery, the large doses required to deliver this benefit (39.5 $\pm$ 8.4 $mg \cdot kg^{-1}$) created some unwanted side effects, particularly involving the heart.[23] Thiopentone exerts a negative inotropic action,[29,30] thus more inotropic support had to be given to patients in the thiopentone-treated than those in the control group.[23] The large doses of thiopentone also led to prolonged sleeping times, delayed extubation of the trachea and an increased degree of sedation over the first three postoperative days.[23] These researchers concluded that the side effects of barbiturate therapy were not prohibitive and that this modality of brain protection was indicated for those operations involving an open ventricle.[23]

The general applicability of the data produced by Nussmeier *et al.* to all patients having cardiac surgery may not be warranted. The study has been criticized on several counts.[31] Firstly, a bubble oxygenator (associated with a higher incidence of emboli than a membrane oxygenator)[32] was used. Secondly, no arterial line filter was used which, although controversial, might have reduced the magnitude of the embolic insult.[33] Finally, hypothermia, which has its own protective effect[34] was not employed. However, the periods of greatest risk for embolic complications (application of the aortic cross-clamp and separation from cardiopulmonary bypass) are usually performed at temperatures above 33° C as pointed out by Nussmeier *et al.*.[23]

Stevenson and Rogers[35] have pointed out two studies which they felt mitigated against barbiturate therapy for brain protection. Contrary to the data of Michenfelder *et al.*,[15,16] Donegan *et al.*[36] demonstrated no dichotomy with respect to the selective ability of barbiturates to reduce metabolic rate vs flow. They showed a parallel reduction in flow and metabolism. This study raises the question as to whether barbiturates preferentially lower metabolism and restore the cerebral oxygen supply/demand ratio.

In the Brain Resuscitation Clinical Trial, thiopentone loading following cardiac arrest was not associated with improvement in outcome.[37] It must be pointed out, however, that barbiturate therapy was initiated after the neurological insult (cardiac arrest). Michenfelder, in an editorial on the therapeutic benefit of barbiturates during cardiac arrest, concluded that since barbiturates selectively reduce the metabolic component associated with synaptic transmission and no synaptic transmission occurs during cardiac arrest, barbiturates would not be expected to have a beneficial effect.[4] Studies wherein the aim is to investigate whether the barbiturates have a protective effect on the brain should administer the agent prior to the cerebral insult as was done in the study by Nussmeier *et al.*

Shanks *et al.*[38] pointed out that the data provided by Nussmeier *et al.* barely reached statistical significance and that if even one patient in the thiopentone group had demonstrated persistent neurological deficits, the conclusions would have been invalid. Resolution of these difficulties must await further studies with larger patient numbers which address these issues.

Global ischaemia

CARDIAC ARREST

The use of barbiturate therapy as brain protection during instances of complete global ischaemia, including cardiac arrest, has been investigated in numerous models without benefit. The Brain Resuscitation Clinical Trial failed to demonstrate any improved outcome due to thiopental therapy following cardiac arrest.[37] This would be a predictable outcome if one considered that barbiturates selectively reduced metabolism associated with synaptic transmission, and would therefore only be effective in the presence of EEG activity.[4] During cardiac arrest, the EEG becomes isoelectric within 20–30 sec and this persists for several minutes after resuscitation.[1]

HEAD TRAUMA

It has been established that barbiturates provide a means of reducing and maintaining intracranial pressure.[9] However, a reduction in intracranial pressure (ICP) does not necessarily mean that there will be a corresponding improved outcome. An earlier study[39] suggested improved neurological outcome as a result of decreased ICP. However, conflicting data is also available from a randomized, controlled clinical study.[30]

Therefore, barbiturate therapy remains an alternative for the treatment of ICP, but until more carefully controlled studies are available should not be expected to improve neurological outcome in patients with acute head trauma.[30,40]

Isoflurane

Isoflurane, a volatile general anaesthetic, has gained in popularity since its introduction in 1982, to the extent that it is the predominant inhalational anaesthetic in use today.[41] Isoflurane is often chosen before the intravenously administered barbiturates to provide anaesthesia because its concentration can be altered easily and its actions rapidly terminated.[42] In addition, isoflurane can produce an isoelectric EEG at a clinically acceptable concentration,[41,43] while causing little myocardial depression, when compared with the other volatile anaesthetics such as halothane and enflurane.[44,45] Although isoflurane causes capacitance vessels to lose tone and total peripheral resistance to decrease, cardiac output is maintained.[44]

Isoflurane produces a relatively stable cardiac rhythm[46] with acceptable haemodynamic variables.[45] In contrast, doses of barbiturates necessary to create an isoelectric EEG produce haemodynamic depression[47] which may be a relative contraindication in patients with unstable cardiovascular disease.

Like many other general anaesthetics, isoflurane has the ability to suppress cortical electrical activity and thus reduce that portion of the $CMRO_2$ that is associated with synaptic transmission.[47] This has been the primary mechanism proposed by which both isoflurane and barbiturates impart their protective effect. For this reason, investigations of isoflurane as an agent capable of protecting the brain from ischaemic injury have been initiated.

Focal ischaemia

The effects of thiopentone, isoflurane and N_2O/fentanyl anaesthesia on neuropathological and neurological outcome in baboons subjected to six hours transorbital left middle cerebral artery occlusion were compared by Nehls *et al.*[42] They were unable to demonstrate any protective effect provided by isoflurane in this model of oxygen deprivation, at least when it was compared with the increased protective effect provided by thiopentone. They concluded that it was not solely the abolition of cortical electrical activity and the reduction of $CMRO_2$ that was involved in providing protection during focal ischaemia. If these two aspects were the only factors involved then isoflurane and thiopentone should have produced similar protection. The reasons for isoflurane's negative result (compared with thiopentone) can be attributed to this agent's vascular effects and its heterogenous reduction of regional metabolic activity.[42]

In contrast to thiopentone's vasoconstrictive properties on the cerebrovasculature, isoflurane is a mild vasodilator.[42] In ischaemic tissue, the vasculature has lost the ability to autoregulate. Thus perfusion through this area is dependent on blood flow to the arterial side of the infarct. Barbiturates vasoconstrict normal vasculature, redirecting the blood flow to areas that are not vasoconstricted, namely the ischaemic area – a positive redistribution of CBF.[7] This "inverse steal phenomenon" only has protective significance during focal ischaemia with little impact in incomplete global ischaemia or hypoxia. The inverse steal phenomenon is not imparted by the volatile anaesthetics because of their vasodilatory properties.[18;42] Intuitively, with vasodilation of the functionally intact vasculature around an ischaemic area, blood flow would be preferentially distributed away from ischaemic to non-ischaemic areas of the brain ("steal phenomenon").

Isoflurane preferentially reduces the metabolic rate for glucose (CMRG) in cortical structures when compared to that measured in sub-cortical structures.[48] Nehls *et al.* observed a higher degree of infarction in the area surrounding the basal ganglia and the thalamus with a lesser degree of infarction in the cortical layers.[42] Barbiturates such as pentobarbitone have been demonstrated to provide a more uniform depression of cerebral glucose metabolism and as such may be expected to deliver a more uniform distribution of protection.[49]

In light of the above, it is recommended that in those circumstances where pharmacological brain protection for focal ischaemia (strokes, etc.) is desired, barbiturates remain the drugs of choice and should not be discarded in lieu of isoflurane.[41,42] However, this does not imply that the potential for isoflurane as a brain protectant is insignificant and should be ignored. Indeed, circumstances may exist where volatile anaesthesia is preferred to a barbiturate technique and thus isoflurane would prove to be beneficial.

When compared with other volatile anaesthetics, isoflurane has demonstrated superior protection during focal ischaemia.[41] Michenfelder *et al.* compared the frequency of cerebral ischaemia during carotid endarterectomy (a model of transient incomplete regional ischaemia) when isoflurane, enflurane and halothane were used.[41] This retrospective study confirmed that different volatile anaesthetics differ in their cerebral vascular properties. More specifically, halothane is the most potent cerebral vasodilator followed by enflurane and then isoflurane. In addition, the critical CBF (that blood flow below which the majority of patients developed ipsilateral EEG changes of ischaemia within three minutes of carotid occlusion) is lowest for isoflurane ($10\ ml \cdot 100\ g^{-1} \cdot min^{-1}$) then enflurane ($15\ ml \cdot 100\ g^{-1} \cdot min^{-1}$) and finally halothane ($20\ ml \cdot 100\ g^{-1} \cdot min^{-1}$).[41] Thus it appears that cerebral vasodilation and critical CBF are related.

Michenfelder *et al.* determined if the lower critical CBF imparted by isoflurane reflected a cerebral protective effect in those patients who did not exhibit EEG changes during the ischaemic period.[41] Cerebral protection could not be measured in direct terms of neurological outcome as those patients who developed EEG changes associated with ischaemic damage immediately had a vascular shunt placed to prevent neurological damage. Therefore, as a measure of neurological outcome and thus an appropriate indicator of possible brain protection, the investigators designated the frequency of EEG ischaemic changes as being a legitimate variable.[41] The EEG ischaemic changes are thought to be part of a continuum that is initiated by carotid occlusion and may or may not progress to severe neurological damage and death, depending on whether therapeutic intervention occurs.[41] The results of this study clearly demonstrated a significantly lower incidence of EEG ischaemic changes with isoflurane anaesthesia (18 per cent) than with either enflurane (26 per cent) or halothane (25 per cent). Isoflurane was introduced into clinical practice after halothane and enflurane, and the preoperative risk status of those patients given isoflurane was worse (i.e., patients given isoflurane were sicker) than the risk status of those patients given enflurane or halothane combined.[41] This would have biased the results against isoflurane. Since isoflurane clearly demonstrated a beneficial effect, the authors concluded that among the volatile anaesthetics, isoflurane appeared to offer some cerebral protection during transient incomplete regional ischaemia which is correlated with its ability to reduce the critical CBF.[41]

Global ischaemia

In a canine model of incomplete global ischaemia,

Newberg *et al.* demonstrated that, in dogs exposed to three per cent isoflurane, a decrease in cerebral oxygen delivery during the ischaemic period was tolerated better than in the control group.[47] This was reflected by a better ability to maintain the cerebral energy stores (ATP and creatine phosphate) and a lesser accumulation of lactate.[47] They attributed this protective effect to isoflurane's ability to reduce cortical electrical activity with a resultant decrease in $CMRO_2$. They stipulated that this protective effect was only valid in those instances of ischaemia where the decrease in oxygen supply was not sufficient to eliminate electrical activity.[47] Other proposed mechansisms of isoflurane protection are given in Table II.

The cerebroprotective effects of isoflurane in humans with incomplete global ischaemia have not been examined.

TABLE II Mechanisms by which isoflurane may exert a cerebral protectant effect[1,47]

Reduction in synaptic transmission
Redistribution of cerebral blood flow
Suppression of seizures
Suppression of hyperactivity induced by catecholamines
Immobilisation
Anaesthesia with deafferentation

Lidocaine

Global ischaemia

Intravenous lidocaine can provide protection to the ischaemic brain in a number of ways, all of which are related to lidocaine's local anaesthetic properties. The mechanism of action of lidocaine-induced anaesthesia involves the selective blockade of Na^+ channels in neuronal membranes.[50] Depolarization is effectively blocked and thus pain transmission, via nerve impulses, cannot occur.[50]

This blockade of Na^+ channels is also the mechanism by which lidocaine provides protection. At high doses, e.g., 160 $mg \cdot kg^{-1}$, lidocaine, like the barbiturates, abolishes synaptic electrical activity (isoelectric EEG) and thus reduces the $CMRO_2$ by that component of cellular metabolism responsible for synaptic transmission.[51] However, unlike the barbiturates, lidocaine can further reduce metabolism beyond that achieved by eliminating synaptic transmission. It was demonstrated by Astrup *et al.* in a canine global ischaemia model that in the functionally arrested brain (i.e., an isoelectric EEG induced by barbiturates), lidocaine can further reduce the metabolic rate by 15–20 per cent.[51] This further reduction in metabolism was attributed to lidocaine's ability to reduce ion leaks (block Na^+ influx and K^+ efflux) and thus reduce the energy requirement for ionic homeostasis by the Na^+K^+-ATPase pumps.[51]

This overall reduction in metabolism is very important as a component of brain protection because it is the depletion of intracellular energy stores that leads to ischaemic metabolic changes. As ATP energy stores decline during ischaemia, the Na^+K^+-ATPase pumps fail with accumulation of Na^+ intracellularly and K^+ loss to the extracellular fluid.[34] These ion shifts lead to cytotoxic oedema and loss of cell function.

The effects of lidocaine (i.e., metabolic inhibition beyond that achievable with an isoelectric EEG alone and a delay in the ischaemic potassium efflux) resemble those of hypothermia. The effects of lidocaine and hypothermia are additive.[51] Thus, lidocaine may be beneficial as an adjuvant to hypothermic protection during ischaemia and may also prove beneficial under normothermic conditions.[34,51] However, these studies by Astrup *et al.* utilised canine models of complete global ischaemia. Studies involving either a primate or human model of focal ischaemia are awaited before any further conclusions can be established with respect to lidocaine's ability to act as a brain protectant.

Focal ischaemia

Evans *et al.* demonstrated in a cat model that pretreating animals with lidocaine greatly attenuated the rise in intracranial hypertension caused by air embolism.[52] The mechanism of action of lidocaine in reducing intracranial hypertension appears to be through lidocaine-induced vasoconstriction of cerebral arteries which would counteract the excessive vasodilation and increased brain volume that results from air embolism and the resultant focal cerebral ischaemia.[52,53]

Benzodiazepines

The benzodiazepines are a class of drugs that exhibit CNS depressant properties and are primarily used as sedatives, hypnotics, anxiolytics and anticonvulsants.[54] Benzodiazepines appear to act on a receptor closely associated with the receptor for gamma amino butyric acid (GABA). When bound to their receptor the benzodiazepines augment GABA's action on its receptor which in turn results in inhibition of the target neuron.[54] The target neurons of GABA and the benzodiazepines are widespread within the CNS and the effect manifested by benzodiazepine interaction is variable.[54]

Global ischaemia

Marana *et al.* demonstrated that diazepam reduces the incidence and the severity of cerebal damage following open-heart surgery.[55] They attributed this protective effect of diazepam to its ability to reduce cerebral metabolism. When administered in conjunction with

N_2O, diazepam reduced the metabolism to a level comparable to the barbiturates, but without the cardiac depression produced by the barbiturates.[55,56] Diazepam improved the oxygen supply:demand ratio.[56] By its ability to augment GABAergic inhibition of neurons, that component of metabolism associated with synaptic transmission is reduced and the remaining cellular energy charge can be allocated to maintenance of the neuron, an effect similar to the barbiturates. Because diazepam has only mild cardiocirculatory effects and a cerebral protective action similar to that produced by the barbiturates, it could be useful in protecting against cerebral damage during cardiac surgery.[56]

Calcium entry blockers

When one considers the pathological sequelae that arise during ischaemia, i.e., altered ion fluxes that are directly related to pathological Ca^{++} metabolism, the rationale for the use of Ca^{++} channel entry blocking agents (CEB) as protective therapy against cerebral ischaemic damage can be understood. Extensive research has been carried out into the use of these agents for the treatment of cardiovascular disorders. The rationale behind protective therapeutics for cerebral ischaemia is to intervene somewhere along the ischaemic pathological continuum in order to prevent or abort the abnormal physiology. The role of CEB in CNS protection has centred around effects on the cerebral vasculature.

The exact mechanism of cerebral protective action of these agents has not been elucidated but it is presumed to be their ability to reduce Ca^{++} influx across plasma and mitochondrial membranes. The proposed mechanisms by which Ca^{++} entry blockers may exert their protective effects are given in Table III.

The Ca^{++} channel entry blocking agents as a group vary widely in their structures, potencies and tissue-dependent specificities and they display differential effectiveness as cerebral protectants.[57] The activity of these agents appears to be tissue-, organ- and species-specific.[57] The tissue specificity of CEBs can be attributed to the variation that exists among Ca^{++} channels and their interaction with different agents.[57] Organ- and species-specificity can be attributed to the differential distribution of these Ca^{++} channels.[57]

Of the CEBs, three have been studied most extensively as protective therapy against cerebral ischaemia. Only one has been studied in a model of focal ischaemia while all three have been applied to a model of global ischaemia.

Global ischaemia

LIDOFLAZINE AND FLUNARIZINE

The results of studies of the cerebral protective effects of lidoflazine and flunarizine during complete cerebral ischaemia are conflicting and inconclusive.

TABLE III Mechanisms by which calcium entry blocking agents may exert a cerebral protectant effect[1]

Prevention of Ca^{++} entry into cells
Prevention of Ca^{++} sequestration by mitochondria
Alteration in fatty acid metabolism
Vasodilation
Free radical scavenging
Prevention of platelet aggregation
Prevention of increases in blood viscosity

Desphande *et al.* demonstrated a significantly improved histological outcome in flunarizine-treated rats that were exposed to severe incomplete global ischaemia.[58] While they were not able to elucidate completely the mechanism of cerebral protection they were able to eliminate improved cerebral blood flow (CBF) during delayed hypoperfusion, and improved post-ischaemic levels of free fatty acids or high-energy phosphates as the mechanisms.[58] In contrast to this positive study, Newberg *et al.* were unable to demonstrate any benefit of flunarizine treatment in a study of complete cerebral ischaemia in dogs.[59]

Similarly, studies with lidoflazine have focused on its potential use in ameliorating or preventing neurological damage due to complete cerebral ischaemia. Mixed results have been demonstrated.[1,60] Messick *et al.*, in their review of lidoflazine, suggested that the discrepancies that arose between the positive and negative studies may be due to the different methodologies. Specifically, all experiments utilized a canine model but exposed the dogs to varying degrees of ischaemia. Because lidoflazine showed differential efficacy with respect to the severity of the ischaemic insults, there may exist a dose beyond which lidoflazine is not effective.[1] If lidoflazine does deliver a positive effect in improving neurologic outcome after complete cerebral ischaemia, it accomplishes it by a mechanism other than improvement of post-ischaemic CBF as has been demonstrated by Dean *et al.*[61]

NIMODIPINE

Of the CEBs, nimodipine and a similar agent nifedipine are potent vasodilators.[62] Unlike lidoflazine and flunarizine, nimodipine has an effect on CBF particularly after complete ischaemia where it ameliorates post-ischaemic hypoperfusion thus increasing CBF once reperfusion has been established.[63] Even in the non-traumatized brain, nimodipine increases the CBF without increasing the cerebral metabolic rate.[64]

In vitro studies

Kass *et al.* utilized an *in vitro* model to examine the

TABLE IV Potential reasons for the lack of effect of nimodipine *in vitro* as a cerebral protectant might include[65]

Ca^{++} influx into neurons during anoxia is by a nimodipine-insensitive Ca^{++} channel
Anoxic damage is influenced by transmitter release affecting Ca^{++} insensitive receptors
Anoxic damage is influenced by NMDA receptor activation

efficacy of the calcium channel blockers nimodipine, magnesium and cobalt to protect against neuronal damage due to anoxia. An *in vitro* model was used in order to eliminate any interaction or effect produced by other tissues upon neuronal tissue (e.g., altered blood flow). In this manner, it was possible to determine if a particular agent imparted any neuroprotective effect solely on the basis of blocking Ca^{++} influx into neurons.[65]

The authors found that treatment with either magnesium (10 mM) or cobalt (2 mM) imparted protection to the neurons of the hippocampus, an area selectively vulnerable to ischaemia. This protective effect was manifested as an increased recovery of neuronal transmission after the hippocampal slice had been exposed to anoxic conditions, and when compared to the untreated control group. In contrast, the authors were unable to observe any protective effect of nimodipine treatment.[65]

In addition to examining the hippocampal slice for recovery of neuronal transmission, Kass *et al.* also examined what effect Mg^{++} and nimodipine had on the ATP depletion that occurs as a result of ischaemia.[65] It has been demonstrated that recovery of electrophysiological activity after anoxia is correlated with the degree of ATP depletion.[66] Magnesium, but not nimodipine, was found to reduce this depletion of ATP during anoxia which parallels what was observed in regards to their relative contributions to electrophysiologic recovery of the evoked response (neuronal transmission) following anoxia.[65]

The differential neuroprotective effects delivered by these Ca^{++} channel antagonists can be explained in terms of their relative Ca^{++} channel sensitivity. At least three types of voltage-sensitive Ca^{++} channels have been identified (T, N and L) based on their relative sensitivity to blockade by various calcium entry blocking agents (e.g., dihydropyridines), cadmium, a marine snail venom, and inactivation at various voltages.[62,67] Receptor operated Ca^{++} channels, e.g., the N-methyl-D-aspartate (NMDA) receptor, require activation by a particular neurotransmitter (NMDA in the case of the NMDA receptor) before Ca^{++} enters the cell. The NMDA receptor is not voltage-dependent but behaves as such under normal physiological conditions. This is due to a voltage-dependent block of the channel by Mg^{++} which is relieved as the cell depolarises. Magnesium and cobalt are selective for all types of voltage-sensitive and NMDA-activated channels that allow Ca^{++} influx into neurons,[65] whereas nimodipine is only effective in blocking the L-type of voltage-sensitive channels. Potential reasons why nimodipine was ineffective in protecting the neural tissue during anoxia *in vitro* are given in Table IV.

A number of mechanisms have been suggested to account for the neuroprotective effect observed by Kass *et al.* for magnesium. These may be extrapolated to the case of cobalt as these two agents are selective for the same Ca^{++} channel types. One of the primary routes by which magnesium contributes to protection is through maintenance of cellular ATP levels[65] which were previously demonstrated to protect against anoxic damage.[66] This maintenance is achieved through the blockade of presynaptic Ca^{++} channels and subsequent blockade of neurotransmitter release, and/or blockade of an NMDA-glutamate receptor channel which is located post-synaptically.[65] It is presumed that the blockade of Ca^{++} channels in both cases leads to a reduction in neural transmission and thus activity of the post-synaptic neurons. Consequently, sodium and calcium influx as a result of neural transmission is reduced significantly and the cellular energy required to reestablish resting ion distribution is reduced as a result.[65] Thus, with the maintenance of cellular ATP during anoxia, those cellular derrangements that arise from ATP depletion will be delayed or even prevented depending on the duration of the anoxic insult.

Magnesium may also deliver protection through prevention of those cellular derangements that are directly attributed to pronounced Ca^{++} influx and which contribute to anoxic damage.[65] Such derangements include phospholipase activation with resultant membrane destabilization and free radical production.

Nimodipine is effective in blocking Ca^{++} influx into cells of the vasculature and reduces the occurrence of post-ischaemic hypoperfusion.[68] It is likely by changes in cerebral flow rather than alterations in Ca^{++} metabolism that nimodipine's neuroprotective effect, if any, is delivered, although blockade of Ca^{++} influx into neurons has recently been suggested.[69]

The results obtained in this *in vitro* model employed by Kass *et al.* are useful in illustrating mechanisms of protection and many of the principles may apply in *in vivo* and clinical models. However, these agents were tested on neural tissue only and any effect on other tissue (e.g., vasculature) or organs was eliminated. Changes in blood flow and perfusion pressure following administration of these agents may produce undesirable effects in other tissues and organ systems. In addition, these agents need not pass the blood brain barrier to reach the neural tissue in this *in vitro* model. If they normally do not cross the blood brain barrier, then their use in *in vivo* models may be

complicated. As such, the information obtained from the *in vitro* model should not be applied to clinical situations until extensive *in vivo* study is pursued.[65]

In vivo studies

Studies in several animal models of complete cerebral ischaemia have shown nimodipine's ability to ameliorate postischaemic hypoperfusion and neurological damage following global ischaemia.[68,70] Whether improvement in neurological outcome can be directly or solely attributed to nimodipine's ability to ameliorate post-ischaemic hypoperfusion has been speculated upon by Steen *et al.*[70] In their study, post-ischaemic treatment with nimodipine was shown to be as efficacious in increasing CBF during the post-ischaemic hypoperfusion period as pre-ischaemic treatment.[70] However, nimodipine was not as efficacious in improving neurological outcome when administered post-ischaemically.[70] This trend suggests that an improvement in post-ischaemic CBF does not necessarily result in improved neurological outcome and that in the case of nimodipine, its beneficial effect may be exerted on events that arise during the complete ischaemic period and not during the post-ischaemic hypoperfusion period as has been generally hypothesized.[70] However, the authors noted that the neurological outcome results were not statistically conclusive[70] and one cannot rule out the significant effect of nimodipine on CBF during the post-ischaemic hypoperfusion period.

Smith *et al.* demonstrated, in a study involving a rat model, that the flow enhancement produced by nimodipine showed marked variability not only among animals but also sometimes creating zones of gross hypoperfusion and overt hyperemia within the same structure.[71] Symon *et al.* also demonstrated a variability in CBF enhancement.[72] Nimodipine not only increased global CBF but produced a redistribution of blood flow in an infarcted hemisphere, leading to an increase in CBF in ischaemic areas and a decrease in hyperaemic areas.[72] This preferential redistribution of CBF by nimodipine may contribute substantially to its protective effect.

A property of nimodipine that proves to be particularly important is its ability to ameliorate post-ischaemic hypoperfusion even when administered up to one hour after a complete cerebral ischaemic insult, comparable to that which occurs during cardiac arrest.[63] Clinical studies by Forsman *et al.* have also demonstrated amelioration of post-ischaemic hypoperfusion with post-insult administration of nimodipine.[73] In patients given nimodipine following resuscitation from cardiac arrest, the CBF was double that of placebo-treated controls.[73] However, unlike Milde *et al.* who suggested neurological outcome may be improved with nimodipine treatment, Forsman *et al.* did not observe any significant difference in outcome between nimodipine-treated and placebo-control patients in their study.[63,73] Randomized, blind, placebo-controlled clinical trials are being conducted to investigate this particular use of nimodipine.[1]

Sub-arachnoid haemorrhage and head injury

Nimodipine has also been applied to the study of sub-arachnoid haemorrhage (SAH) to test its effectiveness in the treatment of vasospasm that arises following head trauma. Allen *et al.* demonstrated a beneficial effect due to nimodipine as the occurrence of neurologic deficits and death were significantly reduced in treated patients.[74] The protective effect was attributed to the inhibition of cerebral arterial spasm by nimodipine.[74] Similarly, another study has shown that nimodipine is efficacious in treating those patients with severe head trauma but without producing adverse changes in ICP or systemic blood pressure.[75]

Focal ischaemia

In studies of nimodipine therapy for treatment of focal ischaemia, studies in animals and man have been encouraging.[57,69,76]

Gelmers studied nimodipine treatment in patients following an acute ischaemic stroke, a form of focal ischaemia.[57] Several diagnostic procedures were used to measure neurological outcome of both treated and untreated patients, including EEG tracings, lumbar puncture, radioisotope brain scans and computerized axial tomography scans. The neurological outcomes were then rated in accordance with the Mathew scale.[77] With all other factors controlled, the nimodipine-treated group displayed greater recovery of neurological function than did the control group.[57] Some clinically insignificant side effects accompanied the nimodipine treatment including a slight decrease in systolic blood pressure and in mean heart rate, probably due to the action of nimodipine upon cardiac tissue. However, these adverse effects were not important enough to prevent utilizing this modality of drug therapy.[57]

In a double-blind, placebo-controlled prospective study, nimodipine significantly reduced mortality from all causes during acute ischaemia stroke in man.[69] During a six-month follow-up, patients in the nimodipine group continued to show significant improvement when compared with the placebo group.[69]

Balanced against the study of Gelmers is the report by Harris *et al.* involving a primate model.[78] In their study, they sought to determine the effects of nimodipine upon the physiological responses of the cerebral vasculature and its possible influence upon focal cerebral ischaemia. Nimodipine severely impaired autoregulation to reduced blood pressure (but not increased blood pressure) and

impaired responses to changes in arterial carbon dioxide partial pressure.[78] These impairments in cerebrovascular physiological responses would be manifested most adversely in ischaemic areas where blood flow is critically reduced.[78] Nimodipine also increased the critical level of CBF at which cytotoxic oedema formation occurred and ion homeostasis was disturbed. Finally, it was found that nimodipine failed to inhibit the reduction in extracellular calcium during ischaemia.[48] More specifically, it failed to block ischaemic Ca^{++} influx.[78,79] This suggested that nimodipine exerted its protective effect by methods other than blockade of Ca^{++} channels.

Despite the adverse effects witnessed by Harris *et al.* in the primate model of focal ischaemia, nimodipine was able to increase (almost double) the post-occlusion CBF.[78] This effect would benefit the cerebral tissue as it would tend to maintain the blood flow above the various ischaemic thresholds including those for loss of electrical activity, ion homeostasis and of formation of ischaemic oedema.[78]

The adverse effects reported with the primate studies can be attributed to species-specific variation in Ca^{++} channels and need not discourage the investigation of nimodipine for treatment of focal ischaemia in humans. However, these results from primate studies suggest caution and further rigorous experimentation in man is required before nimodipine can be suggested for use as a CNS protectant.

Ketamine and NMDA receptor antagonists

Church *et al.* demonstrated the relative neuroprotective action of two phencyclidine receptor agonists, ketamine and MK-801, after transient cerebral ischaemia in rats.[80] These agents readily cross the blood brain barrier and are noncompetitive NMDA receptor antagonists.[80,81] It was found that when MK-801, the more potent and longer acting of the two antagonists, was administered prior to the onset of ischaemia at doses of 0.25 $mg \cdot kg^{-1}$ or 0.5 $mg \cdot kg^{-1}$ a higher degree of protection was afforded when compared with the ketamine-treated group.[80] Ketamine, administered at a dose of 20 $mg \cdot kg^{-1}$ either prior to or following the onset of ischaemia, failed to demonstrate any significant protection.[80] However, when administered at much higher dosages and over an extended period of time following the onset of ischaemia, some protection was observed.

Ketamine possesses a number of properties that prove to be counterproductive as regards neuroprotection.[80] Ketamine increases intracranial pressure,[82] and thus may reduce cerebral perfusion.[83] Ketamine also increases cerebral metabolism in those regions that are selectively vulnerable to ischaemia.[80,84] This would enhance the general metabolic uncoupling that occurs during ischaemia leading to cellular energy depletion. Finally, ketamine influences central transmitter systems other than those of the excitatory amino acid type.[80] Its actions on those other systems may in themselves promote neuronal ischaemic damage or simply mask any beneficial effect that ketamine can deliver through its NMDA receptor antagonism properties.[80]

From their study, Church *et al.* concluded that the systemically administered NMDA antagonists do provide neuroprotection to selectively vulnerable regions of the brain after transient near-complete forebrain ischaemia. However, the doses of ketamine or MK-801 required to impart such a benefit in this study produced significant behavioral disturbances.[80] This is a serious shortcoming if these agents are to be considered as prophylactic treatment during neurosurgery, because accurate neurological assessment is of great importance following surgery.[80] Further work in this area is anticipated as other agents are investigated for their CNS protective effects.

MK-801's greater neuroprotective efficacy may be due to a relative lack of the detrimental features that ketamine possesses thus allowing the protective effect of MK-801's NMDA antagonism to prevail.[80] If this is the basis for the differential efficacies of ketamine and MK-801, then further research should examine other PCP-like NMDA antagonists of a similar nature.[80]

Phenytoin

Global ischaemia

Phenytoin has been shown to possess potential as a brain protectant in several studies of complete global ischaemia. Two separate studies, by Aldrete *et al.* and Cullen *et al.*, demonstrated that treatment with phenytoin improved neurological recovery and reversed histopathological changes in animals subjected to complete global ischaemia.[85,86] The positive effect of phenytoin therapy was supported by a clinical trial involving patients given phenytoin following cardiac arrest. These patients made nearly complete recovery.[87]

Artru *et al.* proposed that the mechanism by which phenytoin exerts its protective effects is through slowing the release of K^+ from ischaemic neurons,[88,89] but it may also contribute by stabilization of cellular membranes. Phenytoin would thereby prevent the ischaemic damage that results from ischaemic redistribution of K^+ (Table V).

The ability of phenytoin to limit cerebral extracellular K^+ accumulation, and thus prevent ischaemic changes that arise from such an accumulation, would improve the distribution of CBF, energy/substrate delivery, and prevent the accumulation of metabolites and toxic substances.[88]

TABLE V Ischaemic changes induced by high extracellular K^+ concentrations[1,87]

Vascular smooth muscle contraction and increased cerebrovascular resistance
Glial swelling resulting in cytotoxic oedema
Direct neurotoxicity

TABLE VI Mechanisms by which corticosteroids may exert a cerebral protectant effect[27,95–102]

Membrane stabilisation
Reduction of oedema formation
Scavenging of free radicals
Reduction in CSF production
Elevation of seizure threshold
Prevention of membrane phospholipid breakdown due to anti-phospholipase effect of lipocortins

Agents with potential but unproven efficacy

Corticosteroids

Corticosteroids have long been known for their anti-inflammatory properties. The corticosteroids can exert their influence at several different levels of the ischaemic continuum including the onset of the inflammatory response. These agents can effectively alter this normal response to injury and may alter the neurological outcome following an ischaemic insult. The inflammatory response which includes such phenomena as oedema, fibrin deposition, capillary dilatation, migration of leukocytes into the inflamed area and phagocytic activity[90] can lead to further cell damage and can prolong or worsen the ischaemic state of certain tissues.

The pathogenesis of the inflammatory response begins with the depletion of cellular energy stores and the subsequent accumulation of intracellular Ca^{++} which leads to activation of phospholipase A_2 and the resultant breakdown of membrane phospholipids.[1] This liberation of membrane phospholipids destabilizes membranes[91] and leads to the production of prostaglandins some of which are chemical mediators involved in inflammation.[92,93] Corticosteroids inhibit the breakdown of membrane phospholipids by stimulating the cells, at the level of genetic expression,[94] to produce lipocortins, a group of proteins that inhibit phospholipase A_2.[95,96] These lipocortins are probably produced by proteolytic cleavage of a macromolecule.[97] Thus with corticosteroid treatment in the event of ischaemia, those phenomena associated with inflammation should be prevented. Indeed, several studies have demonstrated that corticosteroid therapy may have a role in the treatment of cerebral ischaemia (Table VI).

Encouraging results were also obtained by a clinical trial involving double-blind administration of dexamethasone to acute stroke victims.[103] The study concluded that dexamethasone can be a useful adjunct to the treatment of the patient with a severe stroke and that the beneficial effects of steroids are in part due to their ability to decrease brain oedema secondary to massive brain infarction.[103]

While dexamethasone, as with other corticosteroids, crosses the blood-brain-barrier (BBB) bound to albumin,[104] lipocortin is not likely to cross the BBB. Lipocortin can be administered intracisternally and has been shown to increase survival rate and reduce brain oedema in rats subjected to experimental stroke.[102] However, some undesirable side effects of steroid therapy such as teratogenecity[105] might also be mediated by lipocortins. Therefore, the use of lipocortins in human therapy cannot be justified at this time.[102,103]

As with any experimental hypothesis there exist opposing views and experimental findings and such is the case with the effectiveness of corticosteroid therapy. Despite the existence of a few positive studies cited above, the results of several other laboratory studies of focal cerebral ischaemia have demonstrated that corticosteroid treatment of ischaemic brain infarction and oedema in experimental animals and humans has in most instances shown no beneficial affect.[97,106–108]

Corticosteroids are also known to have an effect on the immune system. Many of the chemical mediators produced in the ischaemic cell from arachidonic acid (e.g., 5 HETE (5-S-Hydroxy-6,8,10,14-ercosatetraenoic acid)) are chemotactic to leukocytes and cause these immune cells to aggregate in the area of injury.[109] Corticosteroids block the production of these mediators and thus the aggregation of these cells at ischaemic sites.[92]

Neutrophils are a class of immune cells that are typically present during inflammation as they phagocytise cellular debris that results from the ischaemic insult. Free radicals are often released by these activated phagocytes and may be expected to produce further damage.[110] Low concentrations of glucocorticoids have been shown to inhibit the formation of plasminogen-activating factor by neutrophils.[111] This enzyme is responsible for converting plasminogen to plasmin which in turn is an enzyme that enables leukocytes to enter the inflamed areas by hydrolysis of fibrin and other proteins.[90] In this manner, glucocorticoids inhibit the aggregation of leukocytes at the site of inflammation and also inhibit the penetration of these cells into the site of cell damage.

Whether the influence of glucocorticoids on the immune system can improve the neurological outcome following an ischaemic insult to the brain has yet to be substantiated by laboratory or clinical studies.

Free radical scavengers

The production of free radicals is an inevitable step along the ischaemic continuum and if left unchecked leads to cellular damage and destruction.

Theoretically, damage produced by free radicals may be prevented or decreased with the use of free radical scavengers (barbiturates, vitamins C and E, mannitol, 1-methiamine or glutathione-SH) or with enzymes that promote metabolism of free radicals (catalase, superoxide dismutase).[1,110]

Prostaglandin inhibitors

During reperfusion after an ischaemic event, high levels of arachidonic acid (liberated during ischaemia) are converted into prostaglandins via the cyclo-oxygenase pathway, involving several enzymes including cyclo-oxygenase.[112] Prostacyclin (PGI_2), produced by the vascular endothelium, and thromboxane (TBA_2), produced by platelets, are two very important prostaglandins produced by this catalytic route.[113] PGI_2 is a potent vasodilator and prevents platelet aggregation while TBA_2 is a potent vasoconstrictor and promotes platelet aggregation.[113] Under normal conditions, these prostaglandins act in concert to maintain adequate blood flow through intact vasculature.[1,113] However, during incomplete ischaemia or in the reperfusion period following ischaemia, prostaglandin synthesis is greatly augmented due to increased levels of arachidonic acid and the presence of O_2 which allows for cyclo-oxygenase activity.[1] As by-products of enhanced prostaglandin biosynthesis, increased levels of fatty acid hydroperoxides and other active oxygen species can be expected.[1,114] Hydroperoxides can inhibit prostacyclin synthetase[115] which is responsible for the final step in the production of prostacyclin.[1] If the production of these free radical-like compounds exceeds the normal defense mechanisms of the tissue, they will accumulate and inhibit the synthesis of prostacyclin as well as contribute directly to cellular damage.[1] As a result, an imbalance in the production of PGI_2 and TBA_2 occurs, with TBA_2 production predominating.[1] This imbalance leads to net vasoconstriction and platelet aggregation which may contribute to or produce the post-ischaemic hypoperfusion syndrome.

Indomethacin is a cyclo-oxygenase inhibitor that has been shown to inhibit the increase in prostaglandins that accompanies post-ischaemic reperfusion[116] and to improve post-ischaemic CBF in experimental models of ischaemia.[117]

Iron chelators

During post-ischaemia reperfusion, cellular iron is delocalized from large storage molecules and transferred to a smaller species. It is involved as a catalyst in oxygen-free radical mechanisms that lead to lipid peroxidation which in turn leads to cell damage.[118]

By eliminating iron as a catalyst, lipid peroxidation and cell damage may be prevented. The iron chelator deferoxamine has been shown to inhibit post-ischaemic lipid peroxidation and thus may help to prevent reperfusion injury due to membrane injury by lipid peroxidation.[118] Deferoxamine is considered a safe drug and evidence suggests that it warrants controlled clinical trials to study it further.[118]

It has also been suggested that it be used in conjunction with a Ca^{++} antagonist to ensure post-ischaemic reperfusion and delivery of the iron chelator to ischaemic cells.

Conclusion

We have reviewed some of the pathophysiology of ischaemic brain injury and the pharmacology of cerebral protection. More work is necessary to delineate which pharmacological agent is to be most appropriately used and under what clinical circumstances. Any improvement in therapy will mean better care for our patients because for them, the complications of any central nervous system injury occurring during the perioperative period are devastating.

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