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Review Article

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RECENT TREATMENT OF PARKINSONISM WITH RESPECT TO NEUROPROTECTION

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ABSTRACT

This review concisely compiles the limitations of currently available therapies and the most recent research regarding neuroprotective agents, antioxidants, vaccines and various surgical techniques available and being developed for the management of Parkinson's disease (PD). New approaches designed to attenuate the effects of oxidative stress and to provide neuroprotection of striatal dopaminergic neurons in Parkinson's disease include blocking dopamine transporter by mazindol, blocking NMDA receptors by dizocilpine maleate, enhancing the survival of neurons by giving brain-derived neurotrophic factors, providing antioxidants such as vitamin E, or inhibiting monoamine oxidase B.

Keywords: Parkinson's disease (PD), striatal dopaminergic neurons, levodopa, amantidine, COMT.

INTRODUCTION

Parkinson's disease[1] refers to a neurodegenerative disease that affects several regions of the brain, including the pigmented nuclei in midbrain and brainstem, the olfactory tubercle, the cerebral cortex, and elements of the peripheral nervous system.[2]

PD is a major clinical problem

Parkinsonism describes a syndrome characterised by rigidity, tremor, and bradykinesia, of which Parkinson's disease is the main cause. Parkinson's disease is usually asymmetric and responsive to dopaminergic treatment, with no historical or examination clues to suggest a cause for symptoms. Pathological findings show that nigral dopamine neurons are greatly diminished and Lewy bodies are present in the remaining neurons. Thus, to obtain a definite diagnosis of idiopathic Parkinson's disease, autopsy is needed. A patient's history and examination by skilled clinicians can predict the pathological findings with fairly high assurance. Familial Parkinson's disease and familial Parkinsonism are terms used to describe disease entities with either an autosomal dominant (with variable penetrance) or autosomal recessive pattern. Parkinson-plus syndromes refer to diseases that include Parkinsonism combined with other clinical signs. These include dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.

'Neuroprotection'[3-5] signifies treatments used to protect neural tissue from cellular events induced by deprivation of oxygen or glucose or both to the brain. Neurons are particularly susceptible to ischaemic injury because they have a higher demand for energy and limited energy stores. Depletion of intrinsic central nervous system energy stores occurs within 2 to 4 minutes of anoxia.

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Important strategies in neuroprotection include maintenance of normoxia & adequate cerebral perfusion pressure, maintenance of mild hypothermia, timely surgical intervention & other methods (such as mannitol) to reduce increasing intracranial pressure (ICP), and several methods of pharmacological neuroprotection.

Cellular energy failure threatens cell survival in 3 ways:

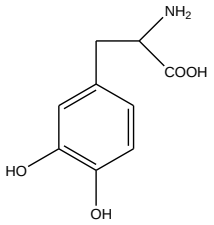
- In the absence of adequate energy stores, anaerobic glycolysis is stimulated, leading to lactic acidosis.
- Energy failure disrupts ion homeostasis. Cellular influx of sodium & chloride with osmotically obligated water and the influx of calcium occur.
- Breakdown of cell structure occurs and is due both to a loss of ATP and to a rise in calcium concentration.

CURRENT THERAPIES AND LIMITATONS OF PARKINSONS DISEASE

There is no cure for PD, since currently available therapies can neither arrest nor reverse the progression of the disease. However, the symptoms can be managed with several different drugs. The drugs used to treat PD either boost the levels of DA in the brain or mimic the effects of DA. Most patients who begin treatment with only a DA receptor agonist eventually will need to add levodopa within a few years. To minimize side effects, very low doses are used initially and gradually titrated up. It is significant to mention here that exposure of patients to the 'gold standard' of PD therapy, levodopa, results in fluctuations of motor responses in approximately 30–50% of patients exposed to therapy for as little as 5 or more years. The most common fluctuation experienced is the so-called 'on–off' phenomenon that results in an unpredictable transient loss of therapeutic effect. Older patients can be particularly sensitive to these drugs, which may cause symptoms of confusion, hallucinations, orthostatic hypotension and fatigue. Apart from levodopa, drugs that are currently prescribed for the management of PD includes DA receptor agonists, selegiline, amantadine,

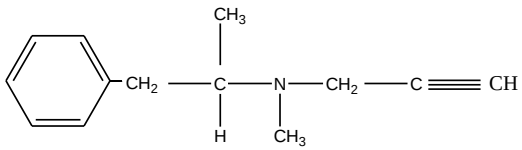
catechol-O-methyl transferase (COMT) inhibitors and anticholinergics. The aim of this paper is to highlight the mode of action and the relative benefits that are observed for the short-lived effectiveness of these agents.[6]

Levodopa



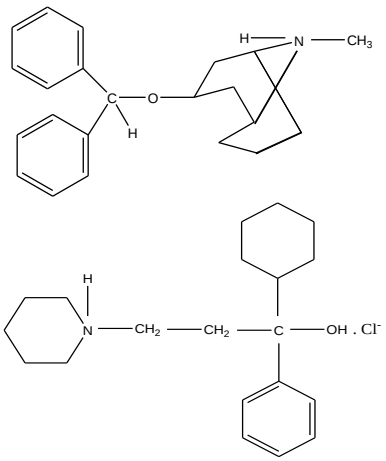
This is the key compound in the treatment of PD, acting as a precursor of dopamine. When levodopa is administered orally it is rapidly decarboxylated and only a small portion of the dose enters the CNS unchanged. Thus a high dose is required for the desired effect which induces nausea and vomiting in patients.

Selegiline



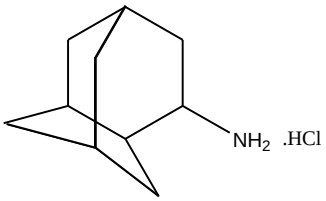
This monoamine oxidase-B (MAO-B)[7] inhibitor prevents the in vivo metabolism of dopamine. As a result when used in combination with levodopa it enhances its antiparkinsonian effects, thus allowing for the dose of levodopa to be reduced. Consequently, its main use is as adjunctive therapy with levodopa. Studies have shown that it may protect neuronal cells from the consequences of oxidative stress and promoting the release of neural growth factors. Concurrent use with levodopa may lead to potentiated side effects and studies do suggest that selegiline may retard disease progression and significantly delay the need for levodopa. However, it has been shown to have only a mild therapeutic effect on the management of PD when used alone.

Anticholinergics



Anticholinergics such as trihexyphenidyl or benztropine are specifically effective against tremor. In a recent review from the Cochrane database, data does not strongly support that anticholinergics have potentially better effects on tremor than on other outcome measures. In addition, these agents have little influence on reducing bradykinesia or akinesia. The side effects of anticholinergics often limit their dosing. Side effects such as confusion, drowsiness, agitation, and hallucinations are common. Effects on memory have also been documented and an increased sensitivity to dementia. Furthermore, abrupt withdrawal leads to precipitation of acute parkinsonian symptoms.[3]

Amantidine

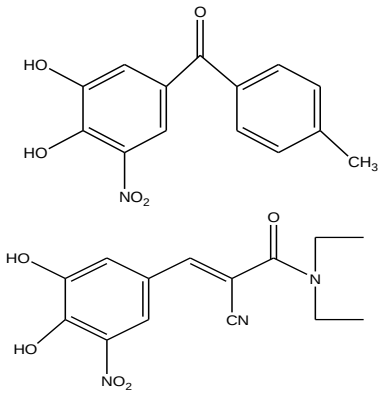


Amantadine[8] an antiviral agent, was found by chance to be effective in PD. Studies regarding the current use of this agent have shown that it is particularly effective in reducing dyskinesias. These effects are thought to be mediated by its anti-glutamate action. Amantadine is thought to either, promote the release, prevent the reuptake, or have an influence on the synthesis of dopamine. Its exact mechanism is still unclear and short-lived and it has the potential to have detrimental effects on cardiovascular disease and even induce seizures in susceptible patients. Its CNS effects include restlessness, depression, confusion and hallucinations.

Dopamine receptor agonists

Dopamine receptor agonists can be divided in two main classes: the ergot derivatives such as bromocriptine, pergolide, lisuride, cabergoline and the non-ergot derivatives such as for levodopa, or may be used with levodopa to increase their effectiveness. Some studies have suggested that these agents may be neuroprotective. The ergot derivatives have the potential to cause psychiatric disturbances and cardiovascular problems that can progress to myocardial infarctions and subsequent death. Even at lower doses patients experience orthostatic hypotension, constipation, dyskinesias, confusion and insomnia with these agents.[9]

COMT inhibitors



COMT inhibitors are used mainly in combination with levodopa. Examples of COMT inhibitors include entacapone and tolcapone. The incidence of sleep disturbances, orthostatic hypotension, dyskinesias, confusion and insomnia are common with these agents. Entacapone, provides a valuable therapeutic tool for the management of PD with regard to motor fluctuations.

Biodegradable polymers such as polylacticco-glycolic acid (PLGA) have been employed to formulate microparticles to deliver drugs such as levodopa (with and without a decarboxylase inhibitor), and DA to the brain via striatal implants. However results of such studies have not been significantly promising since they fail to show sufficiently significant improvement of symptoms in a practically applicable range of time. More recent studies have evaluated the benefit of liposomal delivery of levodopa as a prodrug and even the pulmonary route.

The DA receptor agonist apomorphine has also received significant attention towards optimizing its therapeutic profile. Developed systems have ranged from rectal, intranasal, sublingual, transdermal and subcutaneous formulations. It must be noted however that the effects experienced by patients on apomorphine are relatively non-specific and complicated by numerous side effects and difficulties regarding bioavailability due to extensive first-pass metabolism. Consequently, to date, its use has been limited to the management of 'off'-periods from levodopa therapy. Furthermore, the effects of apomorphine are dependent upon the integrity of DA receptors in striatal neurons. Thus in highly progressed cases of PD, such therapy may be of minimal use.

Transdermal drug delivery has been investigated as an attractive option for delivering pulsatile release of PD drugs in order to provide sustained stimulation of DA receptors and maintain more constant therapeutic drug levels. Added advantages such as its non-invasiveness and ease of use make itnan attractive option for patients.[3]

NON PHARMACOLOGICAL TREATMENT UNDER INVESTIGATION

Newer drug delivery systems for PD are increasingly more focused on site-specific delivery of pharmaceuticals. These include the delivery of various newly researched drugs, genes, viruses, and various peptides.

PD vaccine

The involvement of the protein aggregates and accompanying biochemical cascade in its pathogenesis have allowed the development of a potential PD vaccine that is currently in the clinical trial phase. Animal studies of this vaccine conducted by Masliah et al. have demonstrated extremely positive results. The intended vaccine stimulates the immune system to target the abnormal form of the protein a-synuclein which induces the generation of membrane and intracytoplasmic protein aggregates leading to neuronal regeneration. Human trials on the proposed vaccine are currently underway.[10]

Cell transplantation

Transplantation of dopamine-producing neurons to replace those degenerated during the pathogenesis of PD is a promising approach to treatment. Thus far this is the only advancement that has shown the capacity to allow patients to achieve full restoration of their functional capacity. The grafts have shown minimal immunological rejection in recipients and in the most successful trials have even allowed patients to withdraw from levodopa therapy.

To date however, the majority of studies have derived allogenic ventral mesencephalic tissue from human foetuses. This presents, apartfrom the ethical dilemma for procurement, the implication that sources of such tissues are and will be limited and cannot provide a consistent and reproducible response. Furthermore, they are required in substantial quantities to be adequately efficacious. Stem cells as alternative neuronal sources are receiving a great deal of focus in this regard. The rationale being that they can provide an 'unlimited' source of tissue that can be employed to generate mature dopaminergic neurons to innervate the affected striatum.[11]

The most promising recently conducted research in this area demonstrates that bone marrow stem cells and even ordinary epithelial skin cells may possess the potential to be sources of inducible stem cells. Although studies have shown promising results in preclinical trials, generated neurons have survived poorly after transplantation in animal subjects. One of the most difficult hurdles to overcome is the poor rate of graft cell survival. In fact, as many as 90% of the transplanted cells fail to survive following intracerebral graft. Furthermore, few studies have been able to investigate the long term implications of transplantation; thus the safety of such treatment at this stage remains questionable and the commercial potential of this approach is at the moment a distant reality.[12]

Gene therapy [13]

Transplanted neurons in PD patients are a potential target for the development of gene therapy procedures. A variety of different viral and non-viral methods for achieving gene delivery have been described. According to a recent review Chen et al. among the numerous potential genes that have been evaluated for therapeutic efficacy for PD, those encoding tyrosine hydroxylase, guanosine triphosphate cyclohydrolase I and aromatic L-amino acid decarboxylase all allow for an increase in the production of dopamine. The differentiation of these neurons is mediated by agents such as transforming growth factor beta (TGF-b) and bone morphogenic factors (BMPs). Glial cell line-derived neurotrophic factors (GDNF) have thus far proven to be the most promising option available to restore dopaminergic activity in the substantia nigra. Proposed systems have ranged from adenoviral and lentiviral nigrastriatal implants to liposomes. However more recent studies have indicated conflicting results regarding its effectiveness and the emergence of numerous unwanted side effects that have dampened enthusiasm somewhat for its potential in PD treatment. In a controversial case in 2005, a Phase 2 clinical trial employing intraputamenal infusion of GDNF conducted by Lang and colleagues and sponsored by the leading pharmaceutical company Amgen Incorporated (USA) was halted six months into the research due to failure of its 'novel' GDNF to provide sufficient improvement to PD patients. Thus the development of a stem cell that has the capacity to differentiate into dopaminergic neurons as well as produce such factors has much merit. Genes encoding for the vesicular monoamine transporter-2 and glutamic acid decarboxylase have also demonstrated some benefit. Kang et al. investigated found that the enzyme tyrosine hydroxylase, which has been used in earlier studies, functions only when the essential cofactor, tetrahydrobiopterin is present. This implicates the need for the design and delivery of genetically modified cells that can convert levodopa to DA and store it for gradual release. Alternatively, it has been proposed that nanomaterials like nanotubes may be employed therapeutically as ligand carriers or vectors for drug, DNA or gene delivery for PD. However, so far, this technology remains in the experimental stages of development and far from clinical trials or commercial application.[14]

Surgical methods

Prior to the commercial availability of levodopa, treatment for PD emphasized surgical intervention. Such intervention focused on the reduction of tremor, but failed to address the more debilitating symptom, bradykinesia. However, as mentioned previously, pharmacological therapy for PD often becomes inadequate over long-term use and during significantly progressed stages of the disease. The patient's disability increases despite maximal drug management and many patients develop motor fluctuations and dyskinesias. Surgical interventions for PD

have been shown to be beneficial for refractory symptoms. However their role is limited to being the 'means of last resort' due to the high risk of potential complications and limited long-term efficacy. Thalamotomy and thalamic stimulation are considered safe and effective procedures to treat tremor. Pallidotomy and pallidal stimulation primarily reduce dyskinesia, and have minimal effects on bradykinesia and rigidity. Studies indicate that subthalamic nucleus stimulation improves levodopa induced 'off' period function, decreases 'off' time, and reduces dyskinesia. Surgery is considered for people with intolerable adverse side effects from medication, and those patients who have significant cognitive capacity. Recent advances in this field are now being examined with renewed interest due to the advent of new technology in the form of stereotactic neurosurgical procedures, advances in neuro-imaging, and the development of Deep Brain Stimulation (DBS) procedures. Currently DBS is the intervention of choice due to the fact that this technique is potentially safer than other available options. Unfortunately, only about 5% to 10% of PD patients are candidates for surgical intervention. These procedures are generally not recommended for the following patients:

- Patients who do not respond to levodopa;
- the very elderly;
- Patients whose primary symptom is tremor;
- Patients whose predominant symptoms are freezing and falling;
- Patients who have serious medical or mental disorders;
- Patients with parkinsonism (as opposed to idiopathic PD).

It must be noted that, these procedures are not without their potential for complications. Possible adverse side effects of surgery include brain haemorrhage, infarction, seizures, and even death. Equipment malfunctions can include lead breakage or other hardware failure and pulse generator malfunction. Furthermore, even a successful surgical DBS procedure can lead to side effects that include worsening dyskinesia, paraesthesias, speech and gait disturbance. Developments in nanotechnology have indicated the potential for implantable carbon nanotubes and nanochips to be employed in this arena. These systems promise to allow greater safety and precision for the delivery of impulses in the substantia nigra, and therefore reduce side effects the aforementioned problems with regard to surgery and equipment malfunctions. It has been proposed that the need for repeated surgery would be eliminated, as the systems have the potential for stimulations to be externally modulated. Studies are still in preliminary phases of development; however animal studies have yielded exceedingly.[15]

Anaesthetic agents as neuroprotectants

Intravenous anaesthetic agents

Barbiturates: Barbiturates[16] have the greatest potential to protect the brain from ischaemic injury. Early studies in cerebroprotection suggested that barbiturate associated protection is mediated via reduced metabolic demand. Greatest efficacy has been observed when EEG activity remains present during the ischaemic period. Little efficacy was observed when the EEG is ablated during ischaemia. In global total ischaemia or global total anoxia, barbiturates only reduce the rate of ATP fall for the first 20 to 30 seconds. This is because profound ischaemia flattens the EEG in 15 to 20 seconds, after which time the rate of ATP fall will be the same regardless of the presence or absence of barbiturates. This contrast with hypothermia, which prolongs cell survival and reduces the rate of ATP fall in proportion to the degree of hypothermia.

Other potential beneficial effects of barbiturates are reduction of elevated intracranial hypertension, producing favorable redistribution of blood towards ischaemic tissue by constricting the vessels in the non-ischaemic cortex and suppression of abnormal or seizure-like activity. It has also been suggested that barbiturates exert neuroprotective effects through antioxidant or free radical scavenging actions. Barbiturates may also reduce ischaemia induced neurotransmitter release. Inhibition of the release of excitatory neurotransmitters (aspartate, taurine, glutamate & GABA) has been demonstrated even if barbiturates are administered after the period of ischaemia, suggesting that at least some of the benefit occurs after reperfusion.[17]

Barbiturate neuroprotection is likely to be most marked in focal ischaemia where there remains a marginally perfused penumbral zone in which oxygen supply is reduced but synaptic activity is still going on. Cardiac bypass offer a clinical situation more akin to focal ischaemia with the additional opportunity for prophylactic treatment. Convincing evidence for efficacy of barbiturates has been reported in patients with focal brain injury following open-heart surgery and warm cardiopulmonary bypass. Nussmeier et al found reduced neuropsychiatric complications in patients undergoing open-ventricle cardiac surgery when 30-50 mg/kg of thiopentone was administered during bypass. This study used a bubble oxygenator, did not use arterial line filter and did not involve hypothermia.

Phenobarbital may be used for electrical induction of barbiturate coma. It has a serum half life of about 30 hours. It is administered by a loading dose (3 to 10 mg/kg) at 1 mg/kg/min, followed by continuous infusion at 1 to 2 mg/kg/hour. Monitoring of blood level and maintaining it at 25 to 40 mg/ml range may prevent excessive recovery times from barbiturate coma.

Thiopentone is a rapidly acting barbiturate, which is often used if the desired effect is necessary immediately. In this context, doses of 3 to 5mg/kg i.v. will produce transient (<10minutes) burst suppression & blood thiopentone levels of 10 to 30 mg/ml. Following are the various regimens use:

- High initial dose to produce burst suppression on EEG, which may or may not be followed by an infusion. This use is applicable to situations of focal ischaemia. Loading dose consists of 25 to 50 mg/kg. This is followed by an infusion 2 to 10 mg/kg/hr to give plasma concentration of 10 to 50 mg/L. Accumulation occurs & recovery may be prolonged over a period of days before neurological assessment can be made. Nitrous oxide (N_2O) is not used when barbiturates are used for providing midbrain protection. This regimen is usually reserved for high-risk cases. It is preferable that barbiturates be administered prior to vessel occlusion so that it can circulate to the area, which is to become ischaemic. There appears to be a narrow therapeutic window post-insult, during which therapy may also be effective. Treatment upto 2 hours post-insult may be beneficial, but after this time, it may actually be harmful.
- Low initial dose followed by infusion. This regimen is used to control ICP. A dose of 1 to 3 mg/kg i.v. is

followed by an infusion of 0.06 to 0.2mg/kg/min. This regimen is useful in head injuries to decrease raised ICP. Intermittent low doses of thiopentone (1 to 3 mg/kg) will lower ICP & brain bulk during intracranial operations.

- Small bolus dose for short term protection. A dose of 4 mg/kg over 3 minutes produces EEG burst suppression for about 6 minutes. This time is much shorter than the probable period of surgically induced reversible focal ischaemia. It is suggested that the drug may be delivered to the area to become ischaemic prior to clamping. When ischaemia is induced after this, the level would remain high in severely ischaemic areas since the drug would not be washed out of the area. Local protective effects could thus continue longer than the general EEG suppression. N2O is avoided.[18]

Duration of therapy

When used prophylactically, therapy is usually discontinued when the period of potential or actual insult is over. The duration of therapy when instituted after an insult is controversial & has varied from bolus doses to infusions for 24 to 72 hours or more. Injury may last for this period & cerebral edema peaks at 48 hours after an ischaemic injury. Timing of barbiturate therapy: Cerebral protection is best initiated prior to the occurrence of brain ischaemia. Barbiturate therapy appears to provide some Barbiturates that have been shown to diminish infarct size (animal study) when administered after focal ischaemia. A beneficial effect was seen in primates when barbiturates were given upto 120 minutes after middle cerebral artery occlusion. Methohexitone is less frequently used because of the possibility of exacerbation of seizure disorders.

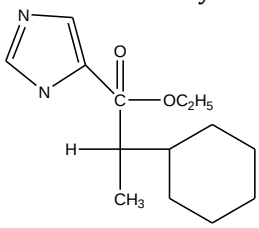
Use in Head Injury

High-dose barbiturate therapy should only be considered for haemodynamically stable salvageable severe head injury patients with intracranial hypertension refractory to maximal medical & surgical ICP lowering therapy. One randomized clinical protocol used a loading dose of 10 mg/kg of pentobarbital over 30 minutes, with 5 mg/kg every hour for 3 doses and maintenance dose of 1 mg/kg per hour. Pentobarbital dose should be adjusted to avoid systemic complications & to achieve an EEG pattern of burst suppression.[19]

Problems during barbiturate therapy

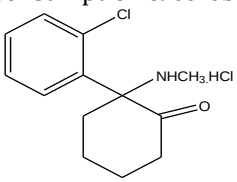
Barbiturate therapy may cause depression of cardiac output & cerebral perfusion pressure, & even cardiovascular collapse in poorly hydrated patients as well as in those with a reduced cardiac function. It is often necessary to reverse hypovolemia & provide pharmacologic inotropic support. Use of cerebral protection with barbiturates may be limited in patients with a reduced cardiac function. The profound respiratory depressant effect of barbiturates makes controlled mechanical ventilation mandatory. Long-term barbiturate therapy is associated with hypothermia & depression of immune responses. This introduces the risk of pulmonary infectious complications. Neurologic evaluation of the patient in barbiturate coma is difficult. The use of intracranial pressure monitoring devices & electro physiologic monitoring coupled with early CT scan, MRI or angiography can help identify adverse developments in a timely fashion. 99% of administered thiopental is metabolized in the liver. Therefore special attention is required in patients with hepatic dysfunction.[8]

Etomidate: Like barbiturates, etomidate produces EEG burst suppression and reduces CMR for glucose and oxygen. Clinically, etomidate decreases CBF, CMRO2 and ICP whereas carbon-dioxide (CO2) reactivity, haemodynamic stability and cerebral perfusion pressure (CPP) are maintained. It inhibits release of excitatory neurotransmitters. It may be useful for neuroprotection when temporary vessel occlusion is required. It is routinely used in some centers to increase safety during temporary arterial occlusion employed for surgery of complex cerebral aneurysms. Doses of 0.4 to 0.5 mg/kg, causes burst suppression in less than 2 minutes in the majority of patients, with a maximum drop in BP of 5%. Consciousness is usually regained in 3 to 5 minutes due to redistribution. Additional doses in increments of 0.1mg/kg may be given as electrical activity returns.



Etomidate has a low incidence of hemodynamic instability at doses sufficient to depress the EEG. In this respect, it has a major advantage over thiopental. However, etomidate has been associated with significant adrenocortical suppression, even when administered as a single injection. This effect of the drug has greatly limited its utility in usual anaesthetic care but not its utility in neurosurgical cases in which patients are routinely administered high doses of steroids. EEG excitation, abnormal movements & vomiting are other adverse effects that could occur. Etomidate has been associated with renal failure presumed secondary to the propylene glycol vehicle.[8]

Propofol: The metabolic changes resulting from propofol anaesthesia closely resemble the homogenous depression of CMR caused by barbiturates and etomidate. Propofol reduces cerebral metabolism with a consensual reduction in EEG activity, O_2 consumption & cerebral blood flow.

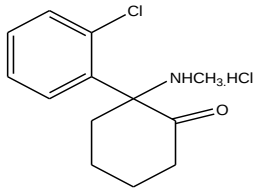


Propofol also reduces voltage-activated sodium channel conductance at concentrations within the clinical range. Its antioxidant properties may also be of benefit. High doses may produce hypotension, which reverses rapidly upon discontinuation (usually within 5-10 minutes). Administration of propofol to head injured patients with elevated ICP has been associated with a reduction in ICP but also of CPP. Propofol infusion titrated to produce unresponsiveness (8 mg/kg/hr) in humans, resulted in 55% depression in CMR for glucose, as measured using positron emission tomography.

A study by J Gilbert Stone et al demonstrated that an EEG suppressive dose of propofol does not depress cardiovascular performance or excessively prolong emergence from anaesthesia when administered in conjunction with DHCA in 13 patients who underwent cerebral aneurysm surgery requiring CPB & DHCA. Before initiating bypass, each patient received propofol: first as a 1 mg/kg bolus, and then by 100 mg/kg per min infusion. The dose was increased every few minutes until the EEG

displayed a burst suppression pattern with a 1:5 ratio. Within 20 minutes, at a propofol infusion rate of between 200 & 300 mg/kg/min, burst suppression with a 1:5 ratio was achieved. The infusion was continued at that rate until circulatory arrest, even though the EEG became isoelectric during bypass cooling. When CPB was resumed, the propofol infusion was begun again at the rate that provided prebypass normothermic burst suppression and continued until the end of surgery. There are reports of possible anaphylactic reaction with angioneurotic edema of the airways. Seizure-like activity has been reported after anaesthesia with propofol.[8]

Ketamine: Following ischaemia, the pathological mechanism which results in cerebral infarction involves the release of a number of neurotransmitters a major one being Nmethyl-D-aspartate (NMDA). Ketamine is a non-competitive antagonist at NMDA receptors & may therefore offer protection from the adverse effects of cerebral ischaemia.



Inhalational agents[6]

Isoflurane: Isoflurane offers a similar level of metabolic depression as barbiturates at a concentration less likely (than barbiturates) to be accompanied by severe cardiovascular depression or prolonged recovery. Isoflurane can suppress brain electrical activity to the point of isoelectricity at clinically useful concentrations (<2MAC). Isoflurane is a potent inhibitor of CMR and CMRO2 in all species studied. In addition to its GABAergic effects, isoflurane has also been shown to inhibit multiple voltage-gated calcium currents in hippocampal pyramidal neurons. Isoflurane has been shown to significantly inhibit glutamate receptor activation and ischaemia induced calcium influx. The majorities of human studies indicate that isoflurane below 1 % has little effect on ICP. Isoflurane at inspired concentrations of 0.6 to 1.1 MAC does not alter CBF although 1.6 MAC doubles CBF. In a study to compare the relative effects of isoflurane, enflurane, and halothane in a human model.[7]

Sevoflurane: In common with isoflurane and barbiturates, sevoflurane produces a dose-dependent decrease in CMR. Auto regulation appears to be well maintained in patients with cerebrovascular disease undergoing sevoflurane anaesthesia. In animal models, sevoflurane not only reduced brain damage following focal ischaemia but also improved neurological outcome following incomplete global ischaemia.

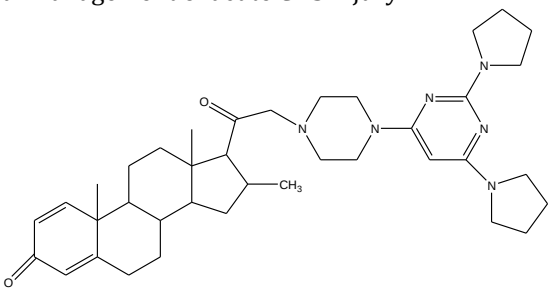
Desflurane: Inhalation anaesthetics such as desflurane can also produce EEG silence but allow a more rapid recovery at the end of surgery. Desflurane treatment for cerebral protection significantly increases brain tissue oxygenation & pH above control levels. Desflurane attenuates hypoxic changes during brain artery occlusion. It also attenuates ischaemic lactic acidosis & decreases in pH during brain artery occlusion. William E Hoffman et al measured brain tissue gases & pH during thiopental or desflurane treatment that was administered for brain protection during temporary brain artery occlusion in patients scheduled for cerebral aneurysm clipping or extracerebral to intracerebral artery bypass. Significant increase in tissue PO2 & pH and decreases in PCO2 were observed during desflurane treatment for brain protection. During brain artery occlusion, tissue PCO2 & pH returned to baseline levels & tissue oxygenation remained elevated in the desflurane group. The enhanced tissue oxygenation & CO2 clearence that is observed with desflurane may be caused by the cerebral vasodilating effect of desflurane compared with thiopental.[8]

Nitrous oxide: Some forms of cerebral protection may be adversely affected by the presence of nitrous oxide (N2O).Nitrous oxide decreases isoflurane's efficacy as a neuroprotectant when used during incomplete cerebral ischaemia in rat.

Non-anesthetic agents as neuroprotectants[20]

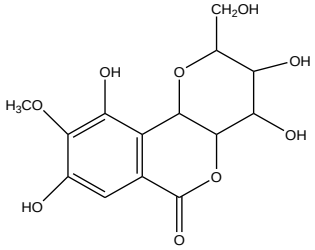
Glucocorticosteroids: Their efficiency in reducing vasogenic peritumoral edema is well documented. The major mechanism for the neuroprotective effect of corticosteroids is probably inhibition of lipid peroxidation. Glucocorticosteroids such as dexamethasone and methyl prednisolone cause or exacerbate hyperglycemia. Hyperglycemia has been shown to increase brain injury in ischaemia. When corticosteroids are used it is essential to maintain precise control of blood glucose levels. The use of glucocorticoids is not recommended for improving outcome or reducing ICP in patients with severe head injury.[8]

Tirilazad mesylate (TM): Tirilazad mesylate (TM) is a 21-aminosterid (lazaroid) that was developed specifically to maximize the inhibition of lipid peroxidation by glucocorticoids such as methyl prednisolone, but eliminate the unwanted glucocorticoids effects. The lazaroids are potent antioxidants, 100 times more potent than the corticosteroids, & therefore may be efficacious in the clinical management of acute CNS injury.



In animal experiments, TM has been of benefit in both focal and global ischaemia with reperfusion. Its mechanism of action appears to be cell membrane preservation by inhibition of lipid peroxidation. Brain levels of the antioxidants vitamin E and, to a lesser extent, vitamin C are preserved in ischaemia-reperfusion, when TM is used. Post ischaemic recovery of extracellular calcium is more rapid with TM use, as is the recovery of intracellular pH and somatosensory evoked potentials.[9]

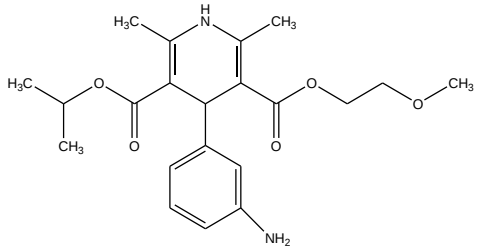
Superoxide dismutase: Superoxide dismutase (SOD) is a specific scavenger of superoxide anion. Superoxide anion is capable of producing significant biological injury. It is generated on reperfusion of post ischaemic tissues.



Because, superoxide dismutase (SOD) has a biological

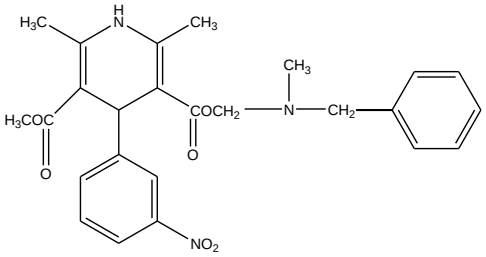
halflife of only 5 minutes, it has been conjugated with polyethylene glycol (PEG-SOD) for use in humans. In a trial of PEGSOD in patients with severe head injury, treatment was a single bolus IV administration, with a mean time from injury to treatment of approximately 4 hours.53 The % of time the ICP was above 20mmHg & the amount of mannitol required to control ICP were less in the moderate dose PEG-SOD (5000 Ukg-1) & high-dose PEG-SOD (10000 Ukg-1) treated patients than in controls. Furthermore, outcome at 6 months was better in the high dose PEG-SOD treated patients (i.e., fewer vegetative or dead).[9]

Nimodipine: This drug antagonizes the entry of calcium into cells, which in turn ameliorates the lactic acidosis, which occurs during ischaemia. Nimodipine probably increases CBF, particularly in regions of moderate ischaemia.



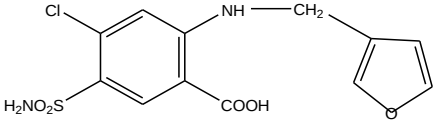
Nimodipine may be particularly effective at neuroprotection during hyperventilation, which is a common intervention during brain surgery. Nimodipine has a beneficial effect on neurological outcome in patients recovering from aneurismal subarachnoid haemorrhage and has become a standard prophylactic therapy in such patients.

Nicardipine: This drug is a calcium antagonist. Cerebral ischaemia causes a rapid shift of calcium from the extracellular spaces into cells. Nicardipine directly reduces calcium entry into ischaemic cells.



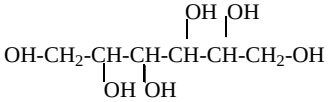
Nicardipine has been administered into venous reservoir before DHCA.

Furosemide: It is a sulfonamide that inhibits distal tubular reabsorption. It has been shown to decrease ICPn effectively without the transient ICP increase that can be seen with mannitol.



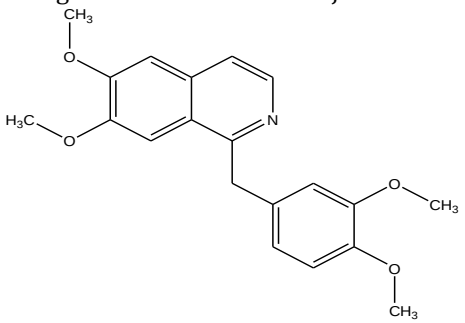
An additional action of furosemide, which may be of benefit, is its reduction of cerebrospinal fluid formation. The dose of furosemide may be upto 1 mgkg-1, depending on the degree of diuresis required.

Mannitol: Mannitol is widely used in neurosurgical operations involving patients with cerebral edema &/or mass effect.



Some of mannitol's potentially beneficial effects include osmotic diuresis, increased blood viscosity & free radical scavenging. Mannitol is used for control of raised intracranial pressure (ICP) after brain injury. It may be given even before computed tomographic scanning, e.g., in patients who develop a fixed, dilated pupil or neurologic deterioration. This agent may also be used when high ICP is demonstrated in the intensive care unit. It should be given as a bolus intravenous infusion, over 10 to 30 minutes, in doses ranging from 0.25 to 1g kg-1 body weight. It is more effective and safer when administered in bolus infusion doses than as a continuous infusion. In patients receiving mannitol, hypovolemia should be avoided, serum osmolarity should be kept below 320 mOsm & serum sodium should be kept below 150 $mEqL^{-1}$. Mannitol has been added to the venous reservoir before DHCA is employe 20 Mannitol is well known to reduce cerebral edema after ischaemia. Mannitol can also scavenge free radicals & thus reduce tissue damage caused by superoxide radicals.

Papaverine: It is a smooth muscle relaxant & may work by blocking calcium channels. It is used for topical application on arteries to reverse vasoconstriction resulting from manipulation (mechanical 'vasospasm'). It has also been given as intra-arterial injection.



However, there is one case report of transient severe brain stem depression during intraarterial papaverine infusion for cerebral vasospasm. Usual concentration used is 30mg in 9cc saline. It is applied on to vessels with gelfoam or cotton pledget soaked in this mixture & left in contact with vessels for 2 minutes. The solution can directly be applied to the vessels with a syringe & left in contact with them. Local application of controlled-release papaverine drug pellets have been safely used in preventing vasospasm. During cerebral aneurysm surgery, drug pellets were placed in cisterns over arterial segments.

Insulin: Elevated intracellular glucose concentration at the time of a cerebral ischaemic insult may result in increased cellular lactic acidosis, & this worsens ischaemic injury. Insulin has been shown to have a neuroprotective effect (Strong et al. 1990)60 and some observations in man are in keeping with these experimental findings (Plum 198361 and Lam et al. 199162).

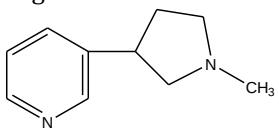
Tromethamine: Tromethamine (THAM), a weak base which crosses the plasma membrane and acts directly on intracellular acidosis has been used with success in models of experimental head injury. THAM has been used in head injuries in man with favorable effects on brain edema and intracranial pressure (Wolf et al. 1993).

Perfluorocarbons: Use of perfluorocarbons is a novel approach to decreasing cerebral emboli associated with cardiac surgery. These compounds have high gas affinity & so may decrease cerebral gaseous microemboli. They may improve flow characteristics in areas of decreased perfusion.

Other drugs: Levy & others have reported a trend toward decreased incidence of stroke in patients receiving high dose aprotinin. The mechanism of action is unknown; however it is tempting to speculate that the anti-inflammatory properties of aprotinin may be responsible. A trial designed to determine the myocardial effects of acadesine, an adenosine-regulating agent, demonstrated lower incidence of stroke in patients receiving the drug. Again, the possible mechanism of action is unknown, but may involve decreased excitatory transmitter release or reduced granulocyte accumulation. Prevention of ischaemic cerebral insults during neurosurgical procedures includes maintenance of cerebral perfusion pressure & use of: Specific pharmacological agents; Chemical brain retractor concept; Hemi dilution; Hypothermia.

Newly researched neuroprotective agents

Nicotine: Recent studies have shown that the principal alkaloid in tobacco, nicotine plays a role in the prevention of agerelated dementias and PD has been one of the diseases given much attention The results have shown that nicotine has a positive impact in preventing the degeneration of neurons in PD. Studies have demonstrated a marked reduction in cortical nicotinic receptor binding that parallels the degree of dementia in PD.



Nicotine, a nicotinic receptor stimulator evokes the release of dopamine from the striatum and therefore protects the nigrostriatal neurons from degeneration. The mode of nicotine addiction is also a possible identification of this mechanism.

A study conducted by clarke demonstrated that nicotine's ability to activate dopamine release in the mesolimbic cortical neurons produces a dependant locomotor (possibly striatal) stimulation. Furthermore, it has been shown that nicotine is able to act as a free radical scavenger and thus prevents lipid peroxidation and subsequent neuronal degeneration resulting in a significant improvement in the patient's mental attentiveness, body control in walking, the use of hands, and reducing anxiety shortly after initiating therapy.

Schneider et al. conducted a study in non-human primates, which demonstrated that the coadministration of a nicotinic agonist with a lower levodopa dose resulted in an improvement in PD similar to that seen with higher levodopa doses, and it led to a decline in motor complications such as dyskinesias. The mechanism of its action is under much debate and investigation. Studies have indicated that this action of nicotine is mediated by the activation of presynaptic nicotinic a4b2 and a7 receptors located on the dopaminergic nerve terminals in the corpus striatum. It has also been shown that nicotine directly induces the neuroprotection of dopaminergic neurons in the substantia nigra by stimulating the release of neurotrophic fibroblast growth factor-2 (FGF-2). The additional effects of nicotine in the brain, such as its ability to selectively stimulate glucose utilization in cerebral neurons, as well as its ability to enhance the production of pituitary hormones that stimulate cortisone production may also shed light on nicotine's mechanism of action.[10]

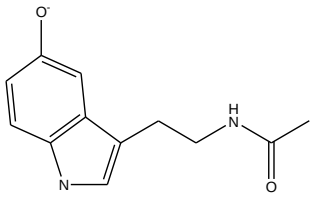
Anti-inflammatory agents: Several factors including inflammation are believed to be involved in the pathogenesis of PD well as inflammatory mediators such as nitric oxide has been reported to be increased in PD. Supporting these findings, the non-selective COX-inhibitor, aspirin and the COX-2 preferential inhibitor meloxicam have been reported to confer neuroprotection in MPTP-induced DA depletion in mice.

Teismann and Ferger evaluated this relationship and demonstrated a positive relationship between aspirin use and progression of MPTP-induced PD. Other COX-activity inhibitors like paracetamol, indomethacin, diclofenac or the steroidal COX expression inhibitor dexamethasone were found to be ineffective in protecting neurons against MPTP neurotoxicity.[10]

Mohanakumar et al. showed that salicylic acid acts as a free radical scavenger in the brain and may be a valuable neuroprotectant. Aspirin, subsequent to its interaction and inhibition of COX is deacetylated to form salicylic acid. On its own, salicylic acid has virtually no in vitro inhibitory activity against free radicals, despite the fact that in vivo studies have demonstrated otherwise. It has been postulated that many actions of salicylic acid have been reported to be independent of the prostaglandin-metabolizing enzymes COX-1 and 2. This therefore suggests that its neuroprotective activity is independent of prostaglandin mediation. Other studies have shown the relationship between the ability of NSAIDs to scavenge free radicals such as the hydroxyl free radical and exhibit a neuroprotective effect.[11]

Sairam et al. evaluated various NSAIDs including sodium salicylate, diclofenac and celecoxib and their neuroprotective effects in MPP^+ induced striatal DA depletion in rats.[11]

Melatonin: Melatonin, a serotonin derivative is a hormone synthesized naturally by neurons in the pineal gland. As the body ages melatonin concentrations decline. It has been investigated for a variety of uses including the management of depression, preventing aging and a variety of cancers. Its current use is limited to the management of jet-leg and the treatment of insomnia, particularly in the elderly. Studies have demonstrated that melatonin has antioxidant properties by acting as a free radical scavenger. It has been shown to cause a considerable dose-dependent reduction in the production of dopaminergic neurodegenerating hydroxyl free radicals.[11]



Monoamine oxidase-B (MAO-B) inhibitors: Rasagiline, a novel MAO-B inhibitor was developed at the University of Minnesota. It is currently being investigated to potentially reduce the progression of PD. It has slightly different properties than selegiline and is effective in alleviating symptoms of PD. Its role as a possible adjunct to levodopa therapy is also being investigated. Currently studies are underway to evaluate various ways in which Rasagiline can be combined with functional moieties that allow for the development of a novel bifunctional compound. It was proposed that this could be done by introducing a carbamate cholinesterase (ChE) inhibitory moiety.[11]

Selenium: Selenium, an essential trace metal is found in the body and forms an important component of numerous

enzymes. Over recent years this metal has been found to be effective in delaying neurodegeneration due to its role in the functioning of the antioxidant enzyme glutathione peroxidase (GSH) which prevents dopaminergic degeneration in the substantia nigra.

Iron-chelators: PD patients have dopaminergic cells with two abnormal structures, a Lewy body and a Lewy neurite. Lewy bodies and Lewy neurites are made up of abnormal aggregates of a-synuclein that lead to darkening of the pigment. Neuromelanin-containing neurons in the brain of healthy individuals do not accumulate this protein, suggesting that the pigment plays a role in the abnormal aggregation of a-synuclein protein in PD. Studies have shown that iron accelerates the aggregation of a-synuclein. Iron converts the ahelical a-synuclein into the b-pleated sheet conformation which contains an inclusion body and various glycated products. An in vitro study employing MPP+- induced PD neuroblastoma cells conducted by Kalivendi et al. concluded that MPP^+ induced iron signaling was responsible for apoptosis of dopaminergic neurons due to the generation of oxidation and protein aggregates (particularly, the aggregation of a-synuclein).[12]

Vitamins A, C and E: The metabolism of DA by MAO enzymes in synapses has been shown to result in a significant rise in the levels of glutathione and its oxidation product, glutathione disulfide. These changes reflect an increase in oxidative stress, most probably attributed to DA oxidation. The role of antioxidants in preventing or even delaying the progression of PD has therefore received much focus. Vitamins A, C and E are all proven antioxidants, capable of preventing lipid peroxidation by acting as free radical scavengers. A comprehensive open study suggested that treatment with high doses of both Vitamin A and C delayed the use of levodopa or DA agonists by 2.5 years.[12]

Other agents: Among other agents that are currently being investigated for their antiparkinsonian effects are phytochemicals such as Ginseng, Ginkgo biloba, chronic lithium therapy, caffeine, cannabis, L-carnitine, estrogen and N-methyl-Daspartate (NMDA) receptor antagonists. The majority of these studies are still in the animal testing stages. Agents such as polyphenols found in Green tea are also in the testing stages. Studies have demonstrated that green tea is at the most a possible adjunct to conventional levodopa therapy for patients and cannot on its own prevent nor treat PD. Ginkgo biloba is an herbal supplement derived from the leaves of the ginkgo biloba tree. It is used for a variety of reasons, but is most often used to improve memory or mental functioning due to flavones. Ginkgo biloba may also have blood-thinning properties and may help to prevent cell damage. Common side effects reported with supplements include an upset stomach, headaches, and dizziness.[12]

CONCLUSION

Neuroprotection involves provision of the means to prevent or minimize injury to neurons. When confronted with the need for neuroprotection, a clear understanding of the underlying mechanisms of both injury and treatment are required to decide on the best approach. Currently available pharmacological therapies are unable to arrest, nor reverse the progression of this relentlessly progressive and severely debilitating condition. The number of individuals afflicted with the disease is constantly increasing due to the increasing global geriatric population. The need for a cure for this debilitating condition is urgent. Many neuroprotective agents investigated offer exciting opportunity for the development of future treatments. The challenge with many of these agents lies in the development of similar or modified versions that are both more selective and potent. Furthermore, the development of drug delivery systems that can effectively deliver these molecules through site-specific mechanisms is vital to optimize their use. Newly developed non-pharmacological technologies, such as the PD vaccine, offer hope to those positively identified with the potential for developing familial PD. The use of pleuripotent stem cells appears to be an exciting avenue as a 'cure all'. However, the identification of alternative sources for cell transplantation from more viable (and ethically sound) sources has thus far limited its practical applicability. The road to developing a cure for this debilitating condition seems far shorter, than it once did.

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