Current and Emerging Treatments in Parkinson's Disease

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Abstract

***Introduction**: Parkinson's disease is one of the commonest neurodegenerative diseases of the elderly. The discovery of dopamine deficiency from the degeneration of substantia nigra neurons revolutionised treatment in the early 70's. **Method**: This review is based on Medline search with Keywords (Parkinson's disease, treatment, therapy, surgery). **Results**: Levodopa remains the gold standard of medications. New drugs include recently introduced dopamine agonists like ropinorole and pramipexole, and COMT inhibitors. The role of selegiline in neuroprotection remains controversial. Dopamine agonist monotherapy may delay the onset of motor fluctuations. Levodopa may be associated with the earlier onset of motor complications such as dyskinesias, and it may be preferable to delay its use in younger patients. In older patients, especially those with significant disability, levodopa use should not be delayed. Surgical therapies such as pallidotomy, bilateral subthalamic deep brain stimulation and foetal transplantation can be considered for those who fail medical therapy. Molecular science techniques including gene therapy, neurotrophic factors, stem cell technology form the next frontier of Parkinson's research. **Conclusion**: No new medication has proven more efficacious than levodopa. More controlled trials are required in Parkinson's surgery to reach definite conclusions about its effects and long-term results.*

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Key words: COMT inhibitor, Deep brain stimulation, Dopamine agonist, Dyskinesia, Pallidotomy

Introduction

Parkinson's disease (PD) affects 1% of adults above the age of 65 years.[1] It is characterised histologically by the loss of neurons in the substantia nigra pars compacta and the presence of Lewy bodies within the degenerating neurons.[2] The clinical syndrome is defined by the presence of tremor, bradykinesia, rigidity and postural instability. A good response to levodopa helps to distinguish the idiopathic form from other causes of parkinsonism such as multiple system atrophy or progressive supranuclear palsy. To clinically differentiate PD from other forms of parkinsonism at an early stage can be challenging. An autopsy series of 100 patients with a clinical diagnosis of PD by a neurologist showed that only 76% had typical Lewy bodies.[3]

Management of Early PD

As there are currently no proven medications to slow down disease progression, most medications provide only symptom relief. Patients should be advised that medications are only required when they have symptoms sufficient to interfere with their normal activities of daily living. There should be an open discussion of the prognosis and treatment options, and the need for exercise and lifestyle adaptations. When medications are required, there are several to consider and these include anticholinergics, selegiline, dopamine agonists and levodopa.

Anticholinergics

The anticholinergic drugs commonly used in Singapore include benzhexol and trihexyphenidyl. These medications have a mild antiparkinsonian effect and although older textbooks often state that they are more effective for tremor than other features of PD, there is no scientific evidence to indicate that there is any difference in tremor effect between anticholinergics and levodopa.[4]

Anticholinergics can cause blurring of vision and are contraindicated in narrow angle glaucoma. They may cause mouth dryness, urinary retention and worsen constipation. The neuropsychiatric side-effects include memory and concentration impairment and it can precipitate an acute confusional state. Because of a relatively wide choice of antiparkinsonian medications, anticholinergics are generally not prescribed to the elderly and the demented.

Selegiline

Selegiline is a non-reversible MAO-B inhibitor. As it does not affect MAO-A, the "cheese effect" which results from ingesting tyramine-rich foods is not seen. The

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DATATOP study (Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's disease) demonstrated that selegiline delayed the need for levodopa, while tocopherol had no effect.[5] Although this was initially thought to be due to a neuroprotective effect, the small but significant symptomatic effect of selegiline negated the assumption of this study. Therefore, its putative role in slowing down neuronal degeneration is controversial, but there is some evidence that selegiline may act through an anti-apoptotic phenomenon.[6] There is also an issue whether selegiline is associated with increased mortality in PD patients. A prospective trial conducted by the Parkinson's Disease Research Group of the United Kingdom showed that there was a 57% higher rate of mortality in the selegiline group,[7] but there were many criticisms of the methodology of the study. Increased mortality has not been seen in other selegiline studies, including DATATOP.[8,9]

Therefore, with respect to symptomatic therapy, selegiline may still be used as a first-line drug for early PD or it can be added on during a later stage because it prolongs the action of levodopa, although it may worsen peak-dose dyskinesias.

Dopamine Agonists

Dopamine agonists act by binding directly to the post-synaptic dopamine receptors, bypassing the nigrostriatal system. Studies show that they can be effective as monotherapy, or as adjunctive therapy in more advanced PD patients. However, they are less potent that levodopa. There are two classes of dopamine agonists: the ergot derivatives, and the newer non-ergoline ones. In Singapore, bromocriptine and pergolide are the most commonly prescribed ergot dopamine agonists for treating PD. The side effects of dopamine agonists include nausea, dizziness, orthostatic hypotension, confusion and psychosis. Domperidone, a peripheral D2-receptor antagonist, is helpful in relieving gastrointestinal symptoms. Uncommon side effects of ergot drugs include pleural or retroperitoneal fibrosis and erythromelalgia, especially when the medications are used at high doses. Piribedil, a non-ergot dopamine agonist which has been available in Europe for several years, was recently introduced in Singapore. Besides its advantage of the avoidance of ergot-related complications, piribedil was shown to have beneficial effects on tremor and depression in patients with PD.[10]

Two new non-ergoline dopamine agonists were introduced in US in 1997, but are not available in Singapore yet. Ropinorole is a highly selective non-ergoline D2 receptor agonist, while pramipexole is a non-ergoline D2 and D2 receptor agonist. Both have been shown to be effective in de-novo and advanced patients.[11,12] Comparing the older and newer dopamine agonists is not easy. One study[12] showed that pramipexole may be more efficacious than bromocriptine and another concluded that ropinorole and bromocriptine were equally efficacious.[13]

As monotherapy, dopamine agonists produce only modest improvement in PD symptoms, but many movement disorder specialists would recommend it as initial therapy to prevent or delay levodopa-induced complications, especially in the younger PD patients. It has been shown that when used alone, dopamine agonists produce less motor fluctuations and dyskinesias, which can be very difficult to treat.[14,15] There is also some evidence that dopamine agonists may be neuroprotective as they can scavenge free radicals and enhance the growth and survival of cultured dopaminergic neurons.

Levodopa

Levodopa, since it was introduced in the 1960s, is still the most effective medication for the treatment of PD. In the early stages of PD, there is a stable, long response to levodopa, but as the disease progresses, the duration of response becomes shorter. This is largely due to continued degeneration of the nigrostriatal neurons with reduced capacity to store dopamine. About 50% of patients develop motor fluctuations after 5 years of levodopa therapy.[16] To smoothen out motor fluctuations such as 'wearing-off', controlled-release preparations of levodopa such as Madopar HBS and Sinemet CR are available. Because of its more sustained action and less pulsatile stimulation of the dopamine receptors, it was suggested that early use of controlled-release levodopa medications may delay motor fluctuations, but the 5-year CR First Study which compared Sinemet CR with standard sinemet failed to show any significant difference.[17]

Some have expressed concern about levodopa being toxic to the remaining neurons of the substantia nigra based on the theory that dopamine is metabolised to form free radicals such as hydroxyl ions. This has led some neurologists to delay the initiation of levodopa. Some *in vitro* studies show that levodopa can be toxic when present in high doses, but these studies were done in the absence of glial cells, which are abundant in the brain, and have a protective role. *In vivo* models are not so convincing of the levodopa toxicity theory.[18] There are some methods of continuous levodopa delivery such as intravenous infusion and intraduodenal continuous infusion which can reduce motor fluctuations significantly, but are not practical for use at the moment.

Should we really delay levodopa? In PD patients less than 50 years of age, levodopa treatment is often delayed for as long as possible. A dopamine agonist is usually initiated and increased gradually until symptom relief is obtained. About 5% to 10% of patients can be maintained

on dopamine agonist monotherapy for up to 5 years. When the patient's symptoms cannot be controlled with dopamine agonists alone, a low dose of levodopa is introduced. This approach delays the onset of motor fluctuations.

In elderly patients, levodopa is started early for symptom relief, as other medications may not be so well tolerated. Anticholinergics are best avoided.

Management of Complicated PD

Motor fluctuations usually occur after 5 years of dopaminergic treatment. The commonest fluctuations are 1) wearing-off, 2) early morning akinesia/foot dystonia and 3) dyskinesias. Dyskinesias can be subdivided into peak dose dyskinesia, diphasic dyskinesia and off period dyskinesia. One recently introduced category of PD medications are catechol-O-methytransferase(COMT) inhibitors.

Catechol-O-methyltransferase Inhibitors

Catechol-O-methyltransferase is an enzyme present in the periphery and the central nervous system. This enzyme breaks down levodopa into inactive forms. By inhibiting COMT, levodopa has increased bioavailability and a longer duration of action.

Tolcapone was the first COMT inhibitor to be introduced in Singapore 2 years ago. Studies show that daily off-time is decreased by 11% to 48% which translates into an improvement of on-time by 1 to 3 hours per waking day.[19,20] Peak dose dyskinesias may be increased, but can be reduced by concomitantly reducing levodopa dosage by 10% to 30%. Severe diarrhoea occurs in about 7% to 10% of those taking tolcapone and may necessitate stopping the medication. A few cases of fatal hepatitis caused a major review of the use of tolcapone.[21] In some countries, the drug has been withdrawn, while in Singapore, 2-weekly liver functions tests have to be performed when the patients is taking tolcapone.

Entacapone, another COMT-inhibitor, was recently introduced in Singapore. So far, there have not been any reports of hepatoxicity due to this drug, and the side-effect of diarrhoea appears to be less common. Like tolcapone, entacapone is administered together with levodopa and has been shown to exhibit similar efficacy to tolcapone.[22]

Wearing-off: This can be managed by giving levodopa more frequently or substituting it with a controlled-released preparation. When using controlled-release levodopa, a 'kick-start' dose of standard levodopa in the morning is usually required. Other approaches include adding a dopamine agonist, selegiline or a COMT-inhibitor. Levodopa is absorbed in the duodenum and this can be antagonised by a high protein meal as amino acids compete for absorption. Giving levodopa before meals and reducing the amount of protein taken during the day can help improve motor fluctuations.[23]

Early-morning akinesia/foot dystonia: On awakening, plasma levodopa levels may be so low as to cause significant bradykinesia or a fixed, painful dystonic spasm of the foot. This is best treated by giving a dose of controlled-release levodopa on retiring at night, or quickly taking a dose of levodopa on waking in the morning and staying in bed until the spasms improve. If these do not help, baclofen may be useful.

Peak dose dyskinesia: These are usually choreic movements, affecting the limbs and occur at the peak of levodopa effect. The dyskinesias are lessened when the levodopa dose is reduced, but often at the expense of increasing periods of off-time. It can be managed by introducing dopamine agonists and gradually increasing it to high doses, while slowly reducing the dose of levodopa.

Diphasic dyskinesias: This is difficult to manage with ballistic movements occurring when levodopa levels are climbing and again when falling. It appears as if the patient has dyskinesias almost the entire waking day. Partial replacement with dopamine agonist is sometimes useful, but liquefied levodopa may have to be employed, giving very small doses at frequent intervals.

New Role for Amantidine

Amantidine is an old medication that has a mild antiparkinsonian effect. Recently, it was demonstrated to have N-methyl-D-aspartate receptor (NMDA) antagonistic properties. In 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) parkinsonian primates, dyskinesias were reduced when NMDA receptors were blocked.[24] Studies show that in PD patients, dyskinesias can be improved by up to 60% without worsening the parkinsonian state by giving amantidine.[25] Other glutamate antagonists being tested include remacemide and riluzole.

Parkinson's Surgery

Resurgence in the interest of surgical treatments for PD occurred in the early 90's when Laitenen reported improvement of all the cardinal symptoms of PD with a lesion placed in the internal portion of the globus pallidus (GPi).[26] MPTP-induced parkinsonian primate models demonstrate that with dopamine deficiency, there is overactivity of the GPi. This overactivity is the result of excessive excitatory glutamatergic input from the subthalamic nucleus (STN). An overactive GPi inhibits the normal thalamic activation of the cortex.[27] By placing a lesion on the GPi, the thalamic inhibition of the cortex is reduced.

MRI and microelectrode recordings of the brain have improved anatomic localisation. Deep brain stimulation

(DBS) can provide a safer and more physiological approach than ablative electrocoagulation. It has also been suggested that gamma knife could be successfully used to treat PD, although symptom improvement is slower than with direct lesioning.[28]

Pallidal Surgery

Lesions in the posteroventral GPi reduce the excessive suppression of the VL thalamus, which projects to the frontal cortex. Several studies have shown improvement in 'off' rigidity, tremor, bradykinesia and especially contralateral dyskinesia.[29-31] Benefit is also seen on the ipsilateral side but not to the same extent as the contralateral side. The improvement on the contralateral aspect may be sustained for two years, but ipsilateral dyskinesias worsen after one year and gait scores are not sustained beyond 6 months. Complications of pallidotomy include visual field defect, internal capsule injury, mild facial paresis, intracerebral hemorrhage and neuropsychological changes, but the incidence of these problems is low. With bilateral pallidotomy, the complication rates are high and these include speech, swallowing and cognitive disturbances. DBS of the pallidum may be a safer alternative to ablation and there are reports of benefit in patients who undergo bilateral pallidal stimulation.[32,33] Interestingly, there may be different responses depending on which part of the pallidum is stimulated. Stimulation of the dorsal portion of the GPi may improve bradykinesia and rigidity, but worsen dyskinesia, while ventral stimulation suppresses dyskinesias but may worsen bradykinesia.[34]

Bilateral Subthalamic Nucleus Stimulation

Bilateral STN stimulation is purported by some movement disorder neurologists to be the most effective functional neurosurgical procedure for PD to date, but a lot more research is required to reach any firm conclusions. It can alleviate most parkinsonian symptoms, including akinesia and gait abnormalities which do not improve much after pallidotomy.[35,36] Global Unified Parkinson's Disease Rating Scale (UPDRS) scores improve by 58% to 88% and many of the patients require less levodopa postoperatively. Dyskinesias are improved secondarily by the levodopa dosage reductions. Transient adverse effects such as parasthesias, dysarthria, diplopia can occur, and there are also reports of more serious complications such as cortical venous thrombosis, thalamic lesions, cognitive decline, intracerebral haematoma and lead infections.[35,36]

In selecting patients for Parkinson's surgery, there are several approaches to the choice of procedure. Those who still respond to levodopa, but experience severe dyskinesias and motor fluctuations are good candidates for pallidotomy or pallidal stimulation. For those with significant axial and gait disturbances, resistant akinesia, bilateral STN stimulation may be a good option. Patients are selected for surgery only after all medication strategies have been tested. Parkinson's-plus patients should be excluded as they do not respond to surgery.[37] Patients with dementia should not be operated on.

Foetal Transplantation

Implanting foetal mesencephalic cells in MPTP-treated primates demonstrate that these cells survive, form connections with host neurons, produce dopamine and cause improvement in motor deficits. Case reports in humans show that there can be significant improvement in 'off' times and UPDRS scores, and fluorodopa positron emission tomographic (PET) scans demonstrate graft survival and function.[38,39] In some patients, levodopa dosage can be reduced. An autopsy study 18 months after transplantation was the first to show large numbers of surviving neurons innervating the host striatum.[40] These case reports show some promising results but ethical issues regarding the use of foetal tissue abound. Even the use of xenografts and cloned cells, when the technology is successful, will have their own moral and ethical dilemmas.

There were two recent National Institutes of Health (USA)-funded placebo-controlled trials of foetal transplantation in North America. The Columbia-Presbyterian-Denver group presented some of their results during an international symposium. Twenty patients received foetal tissue and 20 patients had sham operations. There was significant improvement in those less than 60 years of age, but not in those above 60 years. Tremor and gait scores did not improve in either group. Walking and balance actually worsened in those above 60 years. Graft survival was demonstrated in a majority of patients using fluorodopa PET scans and in 2 autopsied cases. There were a few patients who developed disabling dyskinesias/dystonia (personal communication). At this point of time, foetal transplantation can best be regarded as experimental.

Future Modalities of Treatment

Glial-derived neurotrophic factor (GDNF) promotes the survival of adult neurons in the substantia nigra. In animal models, it can rescue nigral neurons exposed to neurotoxins. Intraventricular administration of GDNF in parkinsonian monkeys improves signs and causes an enlargement of nigral neurons with increased fibre density.[41] A multicentre trial in human PD patients is ongoing in North America.

Immortalised cell cultures imbued with the genes for tyrosine hydroxylase, the rate-limiting enzyme for the production of dopamine, and GDNF are being implanted and tested in animal models. Gene transfer techniques using herpes simplex and adeno-associated viruses have been refined over recent years. Stem cells or neuronal

progenitor cells have been coaxed to express neuronal and glial properties using various cytokines and growth factors. These molecular science techniques form the next frontier of Parkinson's research.

Conclusions

New techniques of treating PD are rapidly advancing. PD is a neurodegenerative disorder with limited areas of cell degeneration and is thus most amenable to a possible cure in the future. Areas of research in gene therapy and cell cloning are promising in this debilitating disease.

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