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Pharmacotherapeutic Approaches of Parkinson's Disease

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Abstract: Parkinson disease is a very common neurodegenerative disease. Most of the drug classes discussed in this review generally acts on the dopaminergic system. Therefore, researchers are attempting to develop drugs which act on non-dopaminergic pathways downstream in the basal ganglia, which are generally involved in the pathophysiology of PD. Compounds that act on noradrenergic, serotonergic, glutamatergic, adenosine, opioid and cannabinoid pathways have been developed so far. Hence, the most preferential symptomatic treatment for PD is levodopa. Due to long-term use, levodopa causes motor complications including involuntary movements and response fluctuations leading to more preferential and cautious prescribing of levodopa. Dopamine agonists can be used as an alternative initial therapy to delay the onset of motor complications but this leads to more dopaminergic adverse events, poorer control of motor symptoms and increased cost. Once motor complications have been developed, adjuvant therapy with dopamine agonists can decrease off time and levodopa dose. Severe fluctuations which are not controlled by oral combination therapy can be controlled with subcutaneous apomorphine injections or infusions.

Key words: Parkinson disease, pharmacotherapy, levodopa

INTRODUCTION

Parkinson Disease (PD) is a common neurodegenerative disease of the central nervous system that often impairs the sufferer's motor skills, speech and other functions (Wright *et al.*, 2010; Jankovic, 2008). By 2040 neurodegenerative disorders (Parkinson's disease), which is presently the second most common neurodegenerative disorder among older adults, affecting approximately 0.5-1% of the population of 60-65-year-olds and 1-3% of over 80-year-olds, may affect approximately 33% of older adults, hence it becomes the second most common cause of death and disability among older adults (Hirsch, 2009).

Onset, which usually occurs at the age of 58 to 60 years and ultimately leads to disability of overwhelming proportions. A significant percentage of patients with PD-10 to 15%-are younger than 50 years. Those who shows symptoms before the age of 20 years are said to have juvenile-onset PD and those who shows PD symptoms at the age of 21 to 40 are said to have young-onset PD. These statistics are unsettling, exclusively for a disease of unknown etiology (Ford-Martin, 2000).

The prevalence of PD in industrialized countries is found to be 0.3% of the general population. The disease increasingly strikes with age which affects about 1% of

65-year individuals and rising to 5% by 85-years of age. The annual prevalence of PD ranges between 16 and 19 individuals per 100,000. PD occurs throughout the world in all ethnic groups and affect both sexes roughly equally or with slight predominance among males. The lowest incidence is reported among Asian and African blacks where as the highest is among European and North Americans. PD generally shortens life-mortality up to 2-5%. PD along with other neurodegenerative diseases is reported to be the second most common cause of death among elderly by the year 2040 (Inamdar *et al.*, 2007).

Parkinson disease is a complex neurodegenerative disorder with both motor and non-motor symptoms. Due to progressive loss of substantia nigra neurons, which generally produce dopamine, neurotransmitter imbalances occur in the basal ganglia. If around 80% of neurons have been lost, Parkinson disease becomes the most evident and patients begin to experience a wide range of difficulties (Yousefi *et al.*, 2009).

PHARMACOTHERAPY

More therapeutic options have recently become available for Parkinson's Disease (PD) leading to significant improvements in motor control both at early and advanced disease stages. More significantly, the need to expand disease management beyond motor

symptom control has been recently highlighted and contribution of non-motor features to quality of life is now relevant (Antonini and Barone, 2008).

NEUROPROTECTION

Neuroprotection in PD can be achieved through antioxidant effects, antiapoptosis, mitochondrial stabilization, glutamate antagonism, adenosine antagonism and anti-inflammatory effects, which are beyond the scope of this review (Ravina *et al.*, 2003). The two most important are coenzyme Q10 and glutathione. Their effectiveness in preliminary studies shows that PD involves a multi factorial process, resulting in degradation of the dopaminergic system. Current thinking demonstrates a complex relationship among several pathogenic biochemical factors. The cascade of events which leads to the eventual destruction of the nigrostriatal dopaminergic pathway may include a combination of free radicals, mitochondrial dysfunction, inflammation and excitotoxicity (Sechi *et al.*, 1996). If this model is used as a cause to PD pathogenesis, it is expected that antioxidant and bioenergetics agents would serve an essential role in protecting this pathway.

SYMPTOMATIC THERAPY

In the absence of neuroprotective therapy for PD, clinicians used to treat the motor and psychiatric symptoms of the disorder. At present, these symptoms are typically mild and include bradykinesia, rigidity and unilateral rest tremor. In many patients disability does not significantly affect function, hence symptomatic therapy can be avoided for 6-18 months (Rajput *et al.*, 1984; Quinn *et al.*, 1986).

EARLY DISEASE

The term early disease refers to patients with newly diagnosed PD or those who have developed functional disability and require symptomatic treatment. Another term used in this context is *de novo* PD (Rajput *et al.*, 1984; Quinn *et al.*, 1986).

Immediate-release levodopa: Dopamine replacement with its precursor levodopa was developed in the late 1960s (Cotzias *et al.*, 1967) but only became into widespread clinical use in the late 1970s and 1980s. Due to the dramatic effects of levodopa on motor disabilities, placebo-controlled clinical trials were considered insignificant. Levodopa generally causes long-term motor complications, including abnormal involuntary

movements (i.e., choreoathetoid dyskinesias and leg dystonia) and motor fluctuations (i.e., predictable end-of-dose deterioration and unpredictable on/off oscillations). These motor complications shows an incidence of 10% per year, so that after 5 years of levodopa therapy about 50% of patients had such problems (Rajput *et al.*, 1984; Quinn *et al.*, 1986).

Anticholinergics: Anticholinergics have been widely used to treat PD for over 100 years and formed the basis of pharmacological management before levodopa became available. Although their mechanism of action is not clear but anticholinergics probably counterbalance the reduced dopaminergic influence on the medium spiny output neurons to the globus pallidus (Katzenschlager *et al.*, 2004).

A recently Cochrane systematic review found nine double-blind, placebo controlled, cross-over trials of anticholinergics in 221 patients with PD. These trials lasted only for 5-20 weeks. Because these studies were done from the 1950s through to the 1980s, numerous outcome measures were used. Trial designs were found to be heterogeneous and they were poorly reported. Hence, no meta-analysis could be done. Nevertheless, every trial demonstrated a positive effect of anticholinergics compared with placebo. As clinical experience has confirmed since the trials, adverse neuropsychiatric and cognitive events occurred in six trials. The reviewers showed conflicting evidence for the effect of anticholinergics on tremor compare with other parkinsonian features (Katzenschlager *et al.*, 2004).

Amantadine: The mechanism of action of amantadine in PD is not known but it is probably a glutamate antagonist. The drug's efficacy for the treatment of motor impairments was discovered serendipitously when it was being used as an antiviral agent. With the development of more effective therapies, such as levodopa and the dopamine agonists, amantadine is not widely used in early PD treatment and dermatological problems (e.g., livido reticularis), confusion and hallucinations have further detracted from its use (Schwab *et al.*, 1972).

MAOB inhibitors: The pharmacology of the MAOB inhibitors and their potential for neuroprotective effects has been discussed. The symptomatic effects of MAOB inhibitor therapy in early PD were the subject of a systematic review that identified (Piccini and Whone, 2004) placebo or active comparator randomized trials of MAOB inhibitor therapy in early PD in 3523 patients. Most trials examined selegiline (n = 13), but there were three trials with lazabemide and one with rasagiline.

MAOB-inhibitor therapy decreased the incidence of motor fluctuations, but not dyskinesia and delayed the need for levodopa therapy. MAOB inhibitors led to greater improvements in UPDRS motor, activities of daily living and total scores than the placebo. There was no report which shows increase in the incidence of adverse events with MAOB inhibitors (Ives *et al.*, 2004).

Dopamine agonists: The symptomatic effects of dopamine agonists in early PD have been summarized in two Cochrane reviews of bromocriptine therapy (Ramaker and van Hilten, 2004) and by the Movement Disorders Society Task Force (Movement Disorders Society Task Force, 2002). The latter concluded that bromocriptine, pergolide, pramipexole and ropinirole were found to be clinically useful in early PD, whereas lisuride was possibly useful and cabergoline was investigational. For the delaying of motor complications, cabergoline, pramipexole and ropinirole were thought to be efficacious, bromocriptine likely to be efficacious and with lisuride and pergolide there was insufficient evidence to comment. Regarding symptomatic control of Parkinsonism, pergolide, pramipexole and ropinirole were rated to be efficacious compared with bromocriptine and lisuride, which were likely to be efficacious and with cabergoline, for which there was insufficient evidence. The adverse effects of dopaminergic drugs were noted with all agonists, but they were all rated to be acceptable without specialized monitoring (Committee on Safety of Medicines, 2002).

LATER DISEASE

In this review, later disease is used to refer those patients with PD who are receiving levodopa therapy and who have developed motor complications. In later disease, adjuvant therapy which aims to reduce off time and levodopa dose while improving control of parkinsonian motor impairments. Motor complications develop within 12 months of levodopa therapy being started in about 10% of patients, so adjuvant therapy may be required soon after levodopa is begun (Deane *et al.*, 2005).

Inhibitors of catechol-O-methyl transferase (COMT): The catechol-O-methyl transferase (COMT) inhibitors decrease levodopa breakdown to 3-O-methyldopa mainly in the periphery and increase the amount crossing the blood-brain barrier. Pharmacokinetic studies have shown that COMT inhibitors increase the area under the plasma levodopa concentration-time curve but not peak levels of levodopa. This is more potentially ideal for patients with end-of-dose deterioration and also peak dose dyskinesia.

Two COMT inhibitors which have received product licences: entacapone and tolcapone. Tolcapone was withdrawn from the European market after three patients died due to hepatic toxicity. It is still available in the USA but the lower dose of 100 mg three times a day is recommended along with intensive hepatic monitoring. A recent Cochrane review of placebo-controlled COMT inhibitor trials found eight trials with entacapone in 1560 patients and six with tolcapone in 1006 patients (Deane *et al.*, 2005). All trials lasted for 12 months or less so inferences about efficacy and safety only apply to the medium term. Entacapone decreased off time and levodopa dose and modestly improved motor impairments and disability. Tolcapone decreased off time and levodopa dose. This was at the expense of increased probability of dyskinesias, nausea, vomiting and diarrhoea with both drugs. A few participants taking tolcapone shows raised liver enzymes. The recent Cochrane review of COMT inhibitors versus active comparators found no trials with entacapone but two trials with tolcapone: tolcapone versus pergolide (n = 203) over 12 weeks and tolcapone versus bromocriptine (n = 146) over 8 weeks (Deane *et al.*, 2004). Tolcapone showed similar benefits to pergolide in levodopa dose reduction, motor impairment and disability and in generic quality-of-life scales (Koller *et al.*, 2001). Tolcapone showed a greater improvement in the disease-specific quality-of-life scale, PDQ-39, than pergolide. Tolcapone showed similar benefits to bromocriptine in off time reduction, motor impairment and disability ratings (Tolcapone Study Group, 1999). Tolcapone showed a greater reduction in levodopa dose than bromocriptine. Nausea, constipation and orthostatic hypotension occur greater with bromocriptine, but otherwise adverse events and withdrawals from treatment were similar with the two classes of adjuvant medication. One patient on tolcapone shows raised liver enzymes, but otherwise the frequency of adverse events and withdrawals from treatment were similar. As tolcapone has been withdrawn from Europe, entacapone is used once motor fluctuations have developed. There are no data available comparing this with other classes of adjuvant therapy, such as agonists or MAOB inhibitors. In recent months, a triple combination preparation of levodopa, carbidopa and entacapone has become available for patients showing motor fluctuations. Patients prefer the triple combination preparation to separate medications (Myllyla *et al.*, 2003). Hence this preference may improve concordance with therapy. Long-term trials of the triple combination versus dopamine agonists and traditional levodopa preparations in early disease are required to assess whether the triple combination can delay the onset of motor complications,

as agonists have been shown to do. Analogous preclinical studies in the MPTP primate model of parkinsonism produced conflicting results about whether entacapone delays the onset of dyskinesia (Jenner *et al.*, 2002; Smith *et al.*, 2003).

MAOB inhibitors: The many adjuvant selegiline versus placebo trials performed in the 1970s and 1980s were less, used various outcome measures and were poorly reported. The Movement Disorders Society Task Force concluded that there was not sufficient evidence that selegiline was effective in patients with motor fluctuations (Movement Disorders Society Task Force, 2002).

An alternative formulation of selegiline that is absorbed through the buccal mucosa is now available; this reduces first-pass metabolism in the liver thereby increasing bioavailability and lowering amphetamine-like metabolites. This formulation decreased off time compared with placebo in a 12 week trial (n = 142) (Shellenberger *et al.*, 2000). However, this formulation of selegiline is found to be more costly than the traditional preparation.

The new MAOB inhibitor rasagiline has already been discussed in *The Lancet Neurology* (Rascol *et al.*, 2003). In a 12 week adjuvant therapy trial in patients with motor complications, rasagiline improved total UPDRS compared with placebo but no details for off time were recorded and no significant change in levodopa dose was found (Rabey *et al.*, 2000). The results of an 18 week trial of rasagiline versus entacapone and placebo in 687 patients with advanced PD and motor fluctuations are reported in abstract form (Rascol *et al.*, 2003). Both drugs significantly decreased off time (both 1.2 h compared with 0.4 h on placebo), increased on time without substantial dyskinesia, reduced levodopa dose (rasagiline by 24 mg day⁻¹; entacapone by 17 mg day⁻¹; placebo increased by 5 mg day⁻¹) and improved activity of daily living and motor scores on the UPDRS.

Few trials which were found to directly compare different classes of drug as adjuvant therapy for advanced PD. Therefore the most effective class of drug is not known and a strategy for the addition of adjuvant agents cannot be formulated. Hence, part of the UK PD MED trial is comparing the effect of adjuvant therapy with dopamine agonists, COMT inhibitors and MAOB inhibitors on quality of life and health economics outcomes.

Amantadine: Amantadine is long established as a treatment of early PD but more recently it has become clearer that it can reduce involuntary movements in advanced disease. A recent Cochrane systematic review

of the trials examining amantadine's antidyskinetic properties found three double-blind crossover trials in 53 patients (Crosby *et al.*, 2004). Carry-over effects cannot be excluded because two trials did not have a washout period and the data from the first halves of the trials were not reported. So, although trial reporters all claimed for a positive antidyskinetic effect of amantadine, the Cochrane review authors felt that no definitive conclusions could be drawn and that further trials are required.

In a randomised, double-blind trial of amantadine versus placebo in 40 patients with PD and dyskinesia, 300 mg day⁻¹ amantadine decreased dyskinesia by 45% (Thomas *et al.*, 2004). However, the useful effects of amantadine lasted for a mean of 4.9 months compared with 1.3 months for the placebo arm (p<0.001). All patients were withdrawn from amantadine treatment within 8 months of commencement due to lack of effect, albeit with a rebound increase in dyskinesia by 10-20% in 11 of 20 patients.

Modified-release levodopa: The Movement Disorders Society Task Force reviewed the trials which compares slow-release levodopa preparations with immediate-release levodopa as adjuvant therapy in PD with motor complications (Movement Disorders Society Task Force, 2002). There was no sufficient evidence of benefit from modified-release levodopa, particularly in the long-term. Clinicians and patients in many of these above trials preferred modified-release levodopa, whereas results in clinical practice have been less convincing due to peculiarities of absorption and thus the unpredictable switch on time with each dose.

Apomorphine: When given orally, the dopamine agonist apomorphine is a powerful emetic. However, when patients are pretreated with the antiemetic domperidone, subcutaneous apomorphine injections and infusions relieve the motor features of PD (Frankel *et al.*, 1990). Subsequent long-term follow-up studies demonstrated that patients can be maintained on apomorphine either intermittently or by infusion for many years (Manson *et al.*, 2002; Tyne *et al.*, 2002). Apomorphine infusions can act in a similar way to bilateral sub thalamic stimulation which allows a reduction in oral medication for PD and thereby decreasing pulsatile stimulation and peak dose involuntary movements (Manson *et al.*, 2002). Apomorphine injections are beneficial for patients with severe PD who have several off periods during the day and have not responded to changes in oral therapy. Apomorphine infusions are strictly prescribed to patients with many off periods or random on and off switching. The drawbacks of apomorphine infusions are the

requirement for parenteral administration and their cost, which can be as high as £10 000 per patient per year for larger doses. New formulations of apomorphine have been investigated and an intranasal formulation will become available in the next few years (Dewey *et al.*, 1996, 1998).

INDIVIDUAL DRUG

Coenzyme Q10: This potent antioxidant appears to be significantly depleted in patients with PD. Also called as ubiquinone, coenzyme Q10 is the electron acceptor for complexes I and II in the mitochondrial electron transport chain. Multiple studies have demonstrated a decrease in complex I activity in PD patients (Sechi *et al.*, 1996). A recent study using high dosages of coenzyme Q10 suggested that this treatment can decrease the progression and significantly slow the worsening of PD. Additional studies which combines coenzyme Q10 with PD treatment, including a phase 2 clinical trial, are under way (Rascol *et al.*, 2003). Coenzyme Q10 can be well tolerated at high doses (Shults *et al.*, 2002). It may reduce the action of anticoagulant drugs, so laboratory parameters should be monitored carefully if these agents are used concurrently.

OTC medication and interaction: Patients with PD should be warned for the possible interactions with OTC medications containing scopolamine and antihistamines. Many of these are used as sedatives. They may cause interaction with some PD pharmacotherapy, leading to duplicate effects and possible toxic responses (Starr *et al.*, 1998).

SURGICAL TREATMENTS

Surgical procedures for PD have been developed largely as medical therapies are not effective over the long term which includes ablation, deep brain stimulation (DBS) and cell transplantation. Surgical ablation techniques, first introduced 50 years ago, are more beneficial now because of the accuracy of image-guided neurosurgery and microelectrode recording techniques. DBS is found to be nonpermanent alternative to ablative procedures. A stimulating lead can be implanted deep in the brain to the desired target (usually the sub thalamic nucleus) (Starr *et al.*, 1998). Cell transplantation effectively uses fetal tissue, which is hypothesized to grow and secrete dopamine. The procedure is still on the experimental stage and in clinical trials (Greene and Fahn, 2002).

FUTURE DEVELOPMENT

The triple combination of levodopa, carbidopa and entacapone has been launched for treatment of PD. The non ergot dopamine agonist rotigotine is found to be highly lipophilic and has been formulated into a transdermal patch. This is the subject of phase III clinical trials after obtaining positive results in phase II studies (Metman *et al.*, 2001; Hutton *et al.*, 2001). By providing continuous 24 h dopaminergic stimulation, the rotigotine patch may be able to decrease motor complications but clinical trials are required.

Most of the drug classes discussed in this review act on the dopaminergic system. However, researchers are attempting to develop drugs which act on non-dopaminergic pathways downstream in the basal ganglia, which are involved in the pathophysiology of PD. Compounds which act on noradrenergic, serotonergic, glutamatergic, adenosine, opioid and cannabinoid pathways have been developed. These have anti-parkinsonian or anti-dyskinetic effects in preclinical models of PD and in some cases early clinical trials have been encouraging (Silverdale *et al.*, 2003). Although these developments are exciting, much is unknown about how and when to use existing therapies. The debate on dopamine agonist versus levodopa in early PD disease continues, if only in older patients, as does that on the class of adjuvant therapy to use in advanced disease. Large pragmatic trials are required to address these issues.

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