Treatment of Early Parkinson's Disease

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ABSTRACT: The early treatment of Parkinson's disease continues to be controversial as our understanding of the etiology of the disease remains incomplete. Ideally an intervention that reverses or protects against further damage to dopaminergic neurons would be initiated once the symptoms of the disease are recognized. Unfortunately, there are no currently available therapies that have been shown to have a major impact on the progression of the disease. However, delaying effective symptomatic therapy beyond a point of significant disability does result in increased mortality. Concerns have been raised regarding the potential toxicity of levodopa on remaining nigral neurons. Although there is little support for this concept, levodopa is associated with important complications. The development of new symptomatic treatments has made the management of early Parkinson's disease even more complex and requires that many different factors be considered prior to initiating therapy in an attempt to minimize current and future disability caused by the disease and its treatment.

R SUM : Traitement de la maladie de Parkinson au d but. Le traitement de la maladie de Parkinson (MP) au début demeure controversé à cause de notre compréhension limitée de l'étiologie de la maladie. Idéalement, une intervention qui répare les dommages subis par les neurones dopaminergiques ou qui protège contre la progression de ces dommages devrait être débutée dès que les symptômes de la maladie sont détectés. Malheureusement, il n'existe pas présentement de traitement disponible dont on ait prouvé l'efficacité sur la progression de la maladie. Cependant, le fait de retarder le traitement efficace des symptômes au-delà du moment où le patient éprouve un degré significatif d'invalidité résulte en une mortalité augmentée. La toxicité potentielle de la lévodopa sur les neurones nigraux restants demeure un sujet de préoccupation. Bien qu'il existe peu d'évidence en faveur de ce concept, la lévodopa est associée à des complications importantes. Le développement de nouveaux traitements symptomatiques a rendu le traitement de la MP au début encore plus complexe. On doit considérer plusieurs facteurs différents avant de commencer le traitement afin de minimiser l'invalidité présente et future causée par la maladie et son traitement.

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When treating any chronic illness one always hopes for therapies that will stop or slow disease progression, improve symptoms and have no side effects. None of the currently available treatments for Parkinson's disease (PD) fulfills this goal and we are therefore left with less than perfect treatment for a slowly progressive neurodegenerative disease. Levodopa remains the most effective symptomatic treatment for PD. However long-term complications develop in up to 50% after five years[1] and there has been longstanding concern that it may be toxic to dopaminergic neurons.[2] For these reasons delaying the use of levodopa, especially in young-onset patients, has become the preferred practice in some movement disorder centers. Drugs such as anticholinergics, amantadine and selegiline provide only mild to modest benefit and with time more potent symptomatic therapy is required for the progressive disability. Dopamine agonists have been shown to be effective in the early stages of the disease as monotherapy; yet levodopa is eventually required in most patients. This review will focus on the treatment of early Parkinson's disease including an evaluation of the increasing trend to initiate therapy with dopamine agonists.

Drugs to Slow Disease Progression

Selegiline, an irreversible inhibitor of monoamine oxidase B (MAO-B), is known to prevent MPTP-induced parkinsonism in animal models.[3] In addition to its MAO-B inhibitory effects selegiline has unique anti-apoptotic properties[4] that could have neuroprotective or neurodegenerative implications. Initial clinical evaluation suggested that this drug did slow the progression of symptoms of idiopathic PD.[5] Although some further evidence has been provided for the neuroprotective effect of selegiline[6,7,] unfortunately the weight of evidence indicates that it does not have a substantial neuroprotective effect and most of the apparent benefit during the first year of treatment is likely due to its symptomatic effects.[8] In addition, it does not delay the development of dyskinesias or fluctuations associated with chronic levodopa therapy.[9] One report[10] has suggested a higher mortality

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with long-term adjunctive selegiline administration, however, this study has been criticized for methodological and statistical flaws.[11,12] Two major limitations were the high mortality rate in all groups, regardless of treatment, which would be unexpected for patients with early, mild PD. Second, approximately 50% of enrolled patients dropped out of the study, with the reasons being significantly different between the groups, which would preclude meaningful interpretation of the outcomes. As well, subsequent studies have not shown a similar increased mortality.[13] High doses of vitamin E have been shown to be ineffective in slowing the progression of disease.[5] Other MAO-B inhibitors are being developed, and it is hoped ongoing current phase III clinical trials (e.g. with rasagiline) will demonstrate a clearer effect on disease progression. Numerous other approaches to neuroprotection are being considered. The major limitation remains our incomplete understanding of both the cause(s) of Parkinson's disease and the mechanisms of cell death that result from these causative factors.

Symptomatic treatment

Parkinson's disease is a progressive disease and since no medications to date have been proven to alter this progressive course, the long-term goal should be to keep the patient functioning independently for as long as possible. In the early stage of PD when symptoms are noticed but not troublesome, symptomatic treatment is not necessary, remembering that all drugs have the potential to induce side effects. In general, most authorities agree that it is appropriate to start treatment when a patient begins to experience functional difficulties that result in reduced quality of life, impairment in the performance of activities of daily living or are a threat to employment status. This decision needs to be individualized as each patient has different views of what constitutes sufficient functional impairment to impact on quality of life. Once the decision has been made to initiate treatment one could consider starting with a less potent (and effective) agent including selegiline, amantadine or one of the anticholinergics.

Amantadine provides mild to modest improvement in about two thirds of early PD patients.[14] Its exact mechanism of action is unclear. It may act by releasing dopamine from the presynaptic terminals or by blocking its re-uptake.[15] More recently, it has been recognized that amantadine is an N-methyl-D-aspartate (NMDA) antagonist[16] and this may be responsible for some of its antiparkinsonian efficacy. NMDA receptor blockade confers a neuroprotective effect in some animal models of parkinsonism[17] and it has been suggested that amantadine improves survival in PD patients,[18] however this is far from proven. It is easy to use and usually well tolerated with leg edema and livedo reticularis being infrequent adverse events. In patients with cognitive deficits it can increase confusion and therefore should not be used. The clearance of amantadine is significantly reduced in patients with renal insufficiency and therefore needs to be used cautiously in these patients. Recently it has also been shown to improve levodopa-induced dyskinesias in the later stages of PD.[19,20]

Anticholinergic drugs such as trihexyphenidyl or benzatropine have been used in the treatment of PD for decades, preceding the availability of levodopa therapy. Their major effect is on parkinsonian tremor with little or no anti-bradykinesia effect.[15] They are useful as monotherapy or as adjuncts to dopaminergic therapy. A large number of side effects limit their use especially in the elderly. The peripheral anticholinergic side effects (dry mouth, constipation, urinary hesitancy and visual blurring) are common and can limit dosing, but it is the central side effects on cognition which increase with age, that preclude their use in patients over 70 (some would lower this cut off to 60 or 65).

Concerns About Early Levodopa Therapy

When greater symptomatic benefit is required, it is well accepted that levodopa is the most effective method of reducing parkinsonian disability. However, with time numerous complications develop in the majority of levodopa treated patients and there has been widespread concern that the drug may be toxic to dopaminergic neurons. The mechanism by which dopaminergic neurons in the substantia nigra degenerate is not known but one hypothesis that has gained widespread endorsement is that of oxidative stress.[21,22] The most commonly suggested mechanism by which levodopa and its metabolites (dopamine and quinone derivatives) could induce toxicity is by contributing to this oxidative stress in cells that are predisposed to injury.[21] Protection from the adverse effects of levodopa by antioxidants in cell culture models is felt to support this theory.[23]

The evidence that levodopa may be toxic is mainly derived from *in vitro* cell culture studies and some *in vivo* animal models.[24] Many *in vitro* models using cultures of isolated neurons have demonstrated that high concentrations of levodopa are toxic to dopaminergic cells.[23,25] However, in co-cultures of glia and neurons this toxic effect is not seen and the predominant effect may in fact be neuroprotective.[26] *In vivo* studies have not demonstrated that levodopa is toxic to normal animals[27,28] and it has been shown to actually prolong the life-span of some mice.[29] Normal numbers of healthy dopaminergic neurons are felt to be capable of rapidly reducing the extracellular levodopa levels after systemic administration. This and the normal storage and metabolism of dopamine by these cells is felt to protect healthy animals from the possible toxic effects of exogenous levodopa. It has been suggested that a "sick" or diseased substantia nigra, as in Parkinson's disease, would not only lack this capability but the compensatory over activity of remaining nigral neurons would further predispose to the toxic potential of levodopa by virtue of the fact that they would be more actively turning over and utilizing dopamine.

One line of evidence to suggest toxicity in an animal model is the poorer survival and neurite growth of transplanted fetal dopaminergic neurons when the host rat is treated with levodopa.[30] However, these changes are reversible after prolonged withdrawal of treatment.[31] A paradigm more akin to the situation found in Parkinson's disease is the evaluation of the effects of levodopa in animals with pre-existing lesions of the nigra. In earlier studies using animals with severe lesions of their nigral dopaminergic cells, the addition of levodopa resulted in increased cell loss.[32] However, in a recent study[33] using rats with a more moderate lesion (felt to be more representative of the dopaminergic cell loss in PD patients) treatment with chronic levodopa did not have a toxic effect on the remaining dopaminergic neurons but instead seemed to promote their recovery.

There are no studies in humans that demonstrate that long-term administration of levodopa damages dopaminergic neurons. Non-parkinsonian patients exposed to levodopa for many years

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have not shown damage to their dopaminergic neurons at autopsy.[34] Human studies have shown that the administration of levodopa reduces the mortality in patients with PD.[35] However, this is probably just secondary to its marked beneficial effect on disability.[36] The symptomatic effects could easily mask any additional damage that the drug may cause to the remaining dopaminergic neurons. With time, many PD patients develop symptoms that are poorly responsive to levodopa therapy such as dysarthria, gait disorders, postural instability, and cognitive dysfunction. Whether levodopa contributes to the development of these symptoms is unknown but it is more likely they are secondary to disease-related degeneration of additional nondopaminergic neuronal systems.[37]

Even if levodopa is not truly toxic to the nigra, its effects on the striatum do result in the development of a variety of complications that become a major therapeutic challenge over time. In the early stages of PD, patients enjoy a long-lasting uncomplicated response following a single dose of levodopa. With disease progression and longer-term treatment patients begin to experience motor fluctuations (i.e., wearing-off, on-off) and a variety of patterns of dyskinesias (i.e., peak-dose and diphasic dyskinesias and off-period dystonia). The pathophysiology of these levodopa-related motor complications are poorly understood and concerns regarding these problems have contributed to the longstanding debate on whether or not levodopa treatment should be delayed.[2,37,38]

Individuals treated with levodopa who have a normal nigrostriatal dopaminergic system (e.g. essential tremor) do not develop dyskinesias even after prolonged exposure[34,39] and, aside from kinesia paridoxica and freezing, Parkinson's patients did not have motor fluctuations prior to the discovery of levodopa. However, these types of motor complications were recognized soon after levodopa was introduced to treat PD and in the past, drug holidays were used in an attempt to reduce levodopa-induced motor complications, suggesting that the effects are at least partially reversible. Unfortunately, patients who develop motor complications rarely obtain sustained relief from them, as exemplified by the experience of some patients treated with duodenal infusions of levodopa.[40] Although these patients experience a widening of the "therapeutic window" with less dyskinesias and off time, after up to four years of continuous infusion dyskinesias return to their pre-infusion level soon after the re-introduction of oral levodopa.

The current dose of levodopa clearly plays a role in the severity of dyskinesias since they improve or resolve on lowering the dose. The duration of treatment also contributes to these motor complications as demonstrated in one study[1] where they increased from 20% in the first five years to 70% after 15 years of treatment. The severity of the underlying nigral degeneration plays an important role as exemplified by the very early development of motor complications in patients who had severe nigral damage as a result of MPTP exposure. Age of onset of the disease also has an effect on the occurrence of these problems. Patients with young-onset PD (under the age of 40) have an increased risk of developing dyskinesias and motor fluctuations[41] and this has encouraged many neurologists to delay the introduction of levodopa as long as possible in this group.

It has been suggested that the motor complications are to a large extent, the result of the pulsatile stimulation of dopamine receptors secondary to the intermittent use of levodopa and its short plasma half-life. This contrasts with the normal tonic physiologic stimulation of striatal dopamine receptors. The pulsatile stimulation of the receptors encourages "downstream" changes in the striatum and beyond and this may be partially due to the effects of glutamate as demonstrated by the therapeutic effects of glutamate antagonists on motor fluctuations in a rodent model[42] and on levodopa-induced dyskinesias in the non-human primate.[43] The role of postsynaptic changes in the development of the declining duration of effect of levodopa (once believed to be exclusively due to the reduced storage capacity of remaining dopaminergic neurons) is supported by the finding that the duration of the clinical effects of the direct dopamine agonist apomorphine also declines concurrently with the development of wearing-off with levodopa.[44,45] In animal models, methods of providing more continuous stimulation of dopamine receptors encourages greater normalization of the biochemical changes found in the basal ganglia as a result of dopamine depletion than when intermittent stimulation is used (intermittent levodopa or a short acting dopamine agonist).[46] Thus, it has been proposed that the development of motor complications in PD should be prevented by treatment that provides a more continuous level of receptor stimulation. The use of sustained release levodopa/carbidopa (Sinemet CR) vs standard levodopa/carbidopa therapy for five years was not associated with a reduction of motor fluctuations.[47] However, the complication rate was unusually low for both groups in this study and despite being a longer acting preparation there is still a pulsatile stimulation of receptors with Sinemet CR. It is not known whether the early combination of levodopa (standard or a controlled release preparation) with a catechol-O-methyl transferase inhibitor (+/- a MAO-B inhibitor) might result in more tonic receptor stimulation and therefore fewer or later motor complications.

A loss of dopaminergic cells and the concomitant use of levodopa are required for the development of motor complications. The severity of PD, disease duration, age of disease onset and the method of administering the drug all seem to play a role but clearly other factors are involved as some patients do not develop dyskinesias or fluctuations despite many years of levodopa therapy.[1] Overall, in PD patients, it remains unknown whether levodopa is completely free of toxic effects on remaining nigral neurons or whether the motor complications seen with chronic levodopa therapy are exclusively the result of levodopa therapy or primarily reflect the progression of the disease. A study by the Parkinson's Study Group and sponsored by the National Institute of Health that is currently underway will hopefully provide some answers to these questions.

Evidence for the Early Use of Dopamine Agonists

The early use of a dopamine agonist is considered advantageous in many ways. For those who subscribe to the oxidative stress theory of cell death in PD, dopamine agonists would reduce the turnover of dopamine in remaining nigral neurons and would not be associated with the further increase in oxidative metabolism of dopamine encouraged by the use of levodopa. For those who believe that levodopa is not truly toxic, there is still an interest in delaying its introduction in an attempt to forestall the development of motor complications. This may be possible since most available dopamine agonists have much longer durations of action than levodopa resulting in a more tonic stimulation of dopamine receptors. Direct-acting dopamine agonists have

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established antiparkinsionian effects and have been used in the treatment of PD for many years, mostly as adjunctive treatment with levodopa in advanced patients already experiencing motor complications. When used in *de novo* patients it is generally acknowledged that dopamine agonists have a lower propensity to cause dyskinesias and fluctuations.[48-50] (The laboratory evidence that they may have advantages over levodopa in the treatment of early PD is reviewed by Blanchet elsewhere in this supplement.)

The older dopamine agonists (bromocriptine and pergolide) are effective as monotherapy but are not commonly used for this purpose. Bromocriptine was shown to be effective as monotherapy more than 20 years ago.[51] Although this has been confirmed in a large number of subsequent studies,[52-55] for many patients a satisfactory beneficial effect lasts less than one year.[50] A few trials[56,57] have shown that a small subset of patients can be managed for more than 5 years on bromocriptine monotherapy. Unfortunately, there is a relatively high non-response rate and adverse events are common.[57,58]

Pergolide has not been extensively studied as early monotherapy. In small, open, uncontrolled trials[59,60] patients achieved short-term benefits similar to those seen with bromocriptine. Given the longer duration of action and the different receptor stimulation profile of pergolide vs bromocriptine, it is unfortunate that a large scale blinded, randomized study comparing pergolide to levodopa as early monotherapy has never been (and probably never will be) performed.

The newer dopamine agonists ropinirole, pramipexole and cabergoline have been shown to be effective as monotherapy in early PD patients[61-63] as reviewed in detail elsewhere in this supplement. It is unknown whether these newer dopamine agonists will result in better long-term efficacy with fewer complications than bromocriptine or pergolide but recently reported longer-term studies show some promise.[64,65] However, levodopa therapy will likely still be required for the majority of patients even with these newer dopamine agonists. Surprisingly, it is not known whether the early use of a dopamine agonist followed (when necessary for declining efficacy) by the addition of levodopa results in fewer or later motor complications than if the drugs are introduced in the reverse order.

Difficulties with dopamine agonists as monotherapy are that they may provide inadequate benefit, usually take longer than levodopa to reach effective doses, are more complex to use with more frequent early side effects and almost always require supplementary levodopa for supervening disability after varying periods of time. The most frequent adverse side effects are nausea and vomiting, postural hypotension, drowsiness, constipation and psychiatric reactions (hallucinations and confusion). The psychiatric adverse events require that caution be used in prescribing dopamine agonists in older patients or in patients with preexisting psychiatric illness. Serious but infrequent adverse events associated with the ergoline dopamine agonists (bromocriptine, pergolide, lisuride and cabergoline) include pulmonary and retroperitoneal fibrosis and erythromelalgia which are unlikely with the newer non-ergot dopamine agonists (pramipexole and ropinirole).

Summary and Recommendations

The symptomatic treatment of PD has improved with the development of new medications but unfortunately there are no currently available treatments that have a major impact on the progression of the disease. In patients whose symptoms interfere with function yet are only mild to moderate, anticholinergic medication (especially if tremor is a predominant feature), selegiline or amantadine can be considered. Age has important impact on this decision. Anticholinergics should be avoided in patients over the age of 65. Even when disability is mild, beyond age 70 it is probably safest to begin levodopa. When mild disability persists despite the above treatment, and certainly when disability is more moderate or severe, dopaminergic therapy should be initiated. Currently there is no convincing evidence in animal models or in humans that levodopa is toxic. However, dopamine agonists may result in less motor complications and therefore may have an advantage over levodopa in the early treatment of patients with PD. Long-term studies of the newer dopamine agonists compared to levodopa as *de novo* therapy are awaited with considerable interest. Until then, we tend to initiate treatment with an agonist in patients under age 60 adding levodopa early in the case of poor tolerance or inadequate benefit or later with waning efficacy. Over the age of 60 to 65 and in the rare situation that a younger patient is in urgent need of rapid benefit we begin treatment with a levodopa preparation. As mentioned, it is not known whether there is an advantage to begin adjunctive therapy (e.g. dopamine agonist, COMT-inhibitor) early in the course of levodopa therapy before the development of motor complications or only after these have developed. Hopefully, future studies will assist in answering the many remaining practical questions that relate to the early treatment of Parkinson's disease.

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