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Optimising levodopa therapy for the management of Parkinson's disease

Abstract Levodopa remains unrivalled in providing symptomatic benefit for the treatment of Parkinson's disease (PD). However, wearing-off and dyskinesia have been associated with chronic therapy using traditional levodopa formulations. The onset of these motor complications arises, in part, due to the limited pharmacokinetic profile of traditional levodopa and not as a direct consequence of levodopa *per se*. Clinical trials addressing these issues have suggested that providing less pulsatile and more continuous dopaminergic stimulation by improving the pharmacokinetic profile of levodopa may overcome the onset of these motor complications. It can, therefore, be suggested that the onset of dyskinesia may be prolonged if levodopa is administered in a more continuous manner by administering it as a combination of levodopa/DDCI and COMT inhibitor.

Key words Parkinson's disease · levodopa · motor fluctuations · CDS

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Introduction

The benefits of levodopa

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is manifested clinically by a resting tremor, rigidity, and bradykinesia [58]. Pathologically, it is characterised by the degeneration and loss of dopaminergic neurones in the substantia nigra. The overall consequence of this is the reduction in the ability of the brain to form, store and regulate the release of dopamine [39, 40], which is essential for the control of motor function.

The introduction of levodopa over 40 years ago was perceived as a breakthrough in discovering an efficacious dopaminergic-replacement treatment for PD [1, 15, 44]. Several attempts have been made to design therapies that ameliorate parkinsonian symptoms beyond that provided by levodopa. However, levodopa has continued to remain unrivalled in providing unsurpassed benefit to virtually all PD patients during progression of their disease [54].

Despite the fact that levodopa is extremely effective, several limitations have been associated with its use. The first of these relates to whether or not levodopa is toxic to dopamine neurones. The second is associated with the onset of motor complications that emerge following chronic therapy with traditional levodopa formulations.

This review challenges the limitations associated with traditional levodopa therapies focusing on those relating to the onset of motor complications, and how their emergence may be prolonged by optimising levodopa administration. The theoretical advantages of achieving more continuous dopaminergic stimulation by optimising the pharmacokinetics of levodopa metabolism will be discussed in relation to the onset of these motor complications.

The limitations of traditional levodopa therapies

Questions regarding the toxicity of levodopa have arisen from *in vitro* studies conducted in the 1990s which demonstrated levodopa to exert toxic effects on dopaminergic neurones [3, 29, 36]. Here, it was suggested that the toxicity of levodopa arises due to the production of reactive oxygen species (ROS) produced fol-

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lowing its auto-oxidation [11]. These ROS have the potential to detrimentally react with essential biomolecules resulting in cell death. However, a majority of these *in vitro* investigations were conducted under conditions not exhibited *in vivo*, thus compromising their validity within the PD patient. For example, the concentrations of levodopa used were higher than the peak plasma concentrations observed within PD patients [4, 12, 26, 27, 30, 32, 36, 42, 47]. In addition, glial cells whose high concentrations of antioxidants and trophic factors combat the effects of ROS were absent from the culture system. To address these issues, the *in vitro* experiments were repeated using concentrations of levodopa found *in vivo* and in the presence of glial cells. The data gathered from these studies showed the converse result; levodopa was not found to be toxic and, in the presence of glial cells, the dopaminergic neurons are actually protected from levodopa toxicity [8, 23, 28].

The question surrounding the relative toxicity of levodopa has also been addressed in clinical trials [48, 69] that investigated the effect of levodopa on the rate of disease deterioration. However, during these trials, the study groups were not compared to placebo; thus, the effect of disease deterioration could not be related to levodopa being toxic or to a protective effect of dopamine agonists. Collectively, these trials have provided inconclusive results as to whether or not levodopa does have a toxic effect in PD [59]. In comparison, the recently conducted ELLDOPA study made a direct comparison between the rate of PD progression in those patients treated with levodopa (150, 300, 600 mg/day) compared to placebo [9].

During the ELLDOPA trial, any changes in UPDRS motor score were assessed following 9 months of treatment with placebo or levodopa. The study revealed less deterioration from baseline in UPDRS motor score in levodopa-treated patients than in the placebo controls and all levodopa groups were seen to have improvements vs. baseline assessment, with the highest dose of levodopa (600 mg per day) showing the greatest improvement (UPDRS –1.4). By contrast, there was a significant deterioration of 7.8 points vs. baseline in the placebo group [9]. These results, therefore, do not support the theory that levodopa is toxic, but are consistent with levodopa having a protective effect as initially suggested from the *in vitro* culture investigations. However, results of neuroimaging studies performed as part of this study indicated that levodopa treatment was associated with a greater rate of decline than placebo in a biomarker of nigro-striatal function.

The ELLDOPA study does not, therefore, resolve the issue of whether or not levodopa is toxic in PD. However, from a clinical perspective, it shows that levodopa is not seen to hasten the progression of PD. Also, it further enhances the notion that the dose of levodopa should be adjusted to fit the requirements of the patient's individual requirements. As expected, the smaller doses of levodopa were less effective than the higher doses. However, the higher doses were associated with the onset of motor complications including dyskinesia, one of the fundamental limitations associated with traditional levodopa therapy.

In the early stages of PD, a large therapeutic window exists where the response to levodopa in controlling parkinsonian symptoms is excellent and the magnitude of the clinical benefit is seen to reflect the dose administered to the patient. During this early stage of disease, parkinsonian symptoms are controlled and motor complications are not apparent as the nigral dopamine neurones have the ability to store and release dopamine so that any fluctuations in plasma levodopa concentration can be buffered. However, with disease progression and chronic levodopa therapy, troublesome motor complications emerge, the onset of which is associated with fluctuations in the plasma levels of orally administered short-acting drugs, such as levodopa. Due to the progressive loss of dopamine terminals associated with the progression of PD, these fluctuations in plasma levels cannot be adequately buffered resulting in the dopamine receptors being stimulated in a pulsatile manner. Thus, transient stimulation results in further disruption of an already abnormal motor control network [6, 10, 39, 40, 43], leading to the emergence of levodopa-induced motor complications [43].

The first motor complication observed is 'wearing-off', which can emerge within 1–3 years of initiating treatment [2]. Indeed, the symptoms of wearing-off have been shown to affect nearly half (45 %) of the patients diagnosed with PD within 5 years of initiating traditional levodopa therapy [49, 55]. Wearing-off is characterised by the re-emergence or worsening of parkinsonian symptoms before the next scheduled dose of levodopa takes effect [25, 49, 53] and may be accompanied by involuntary movements such as dyskinesia that occur as the plasma concentrations of levodopa reach their peak. Several subtle non-motor symptoms, including mood changes, pain, cognitive changes such as mental slowing and sensory problems, panic attacks and anxiety are also associated with wearing-off [14, 71] and can greatly impact on the patient's quality of life.

Overcoming the limitations of traditional levodopa therapies – improving the delivery of levodopa to achieve more continuous dopaminergic stimulation (CDS)

It has been proposed that therapy with dopaminergic agents that provide a more continuous and less pulsatile stimulation of dopamine receptors may have the potential to reduce the risk and increase the time to onset of treatment-induced motor complications [7, 39–41, 43].

In the clinic, the importance of CDS has been substantiated from continuous independent infusion studies of both levodopa [31] and dopamine agonists (lisuride or apomorphine) which have been shown to maintain antiparkinsonian activity while concomitantly reducing both the severity and occurrence of dyskinesia [60, 61, 63]. However, these infusion approaches have inherent practical limitations in that they are neither convenient nor easy to manage from the perspectives of both the physician and patient. Therefore, optimising the administration and delivery of levodopa to the PD patient, to provide less pulsatile dopaminergic stimulation, is an important and desirable clinical need.

It is widely accepted that during the progression of PD, it becomes increasingly difficult to deliver a dose of levodopa that provides adequate antiparkinsonian control without inducing dyskinesia [62]. At this stage of disease, patients regularly cycle between periods where they are 'on' and experience dyskinesia, and 'off' periods where they exhibit parkinsonian symptoms [62]. Eventually, there comes a time when the levodopa-induced motor fluctuations are seen to mirror the plasma profile of the drug, suggesting that their onset correlates with the pharmacokinetics of levodopa metabolism. With that in mind, one of the most important goals for chronic levodopa therapy is that it is delivered in a manner that increases its bioavailability to prolong the duration of symptomatic efficacy from each dose without inducing dyskinesia. To do this, the pharmacokinetic limitations of levodopa have to be considered and overcome.

Intraintestinal levodopa infusion

We confirm [67], in an open label trial, earlier reports indicating that continuous intraintestinal infusion of levodopa reduces motor complications in advanced PD patients. We observed that in comparison to a standard oral formulation of levodopa, continuous levodopa infusion significantly improved the number of 'off' hours, the number of 'on' hours without dyskinesia, and dyskinesia severity.

In three patients, pharmacokinetic studies were performed at baseline, when they were receiving a standard oral formulation of levodopa and had severe motor complications, and then again at final visit after 6 months of levodopa infusion, when motor complications were significantly improved. They demonstrate that levodopa infusion avoids the low trough levels observed with oral delivery of a standard formulation of levodopa, and that mean plasma levodopa concentration and area under the curve (AUC) are significantly increased despite the improvement in dyskinesia.

Our study further illustrates that motor complications can be reversed by continuous administration of the same dopaminergic agent that induces them when administered in a pulsatile manner.

We postulate that the low trough levels seen with intermittent administration of standard oral formulations of levodopa cause striatal dopamine receptors to be periodically deprived of dopaminergic stimulation with consequent changes in intracellular signals and neuronal firing patterns leading to motor complications. In contrast, levodopa infusion avoids low plasma trough levels and may, thus, result in more constant activation of brain dopamine receptors with a reduced risk of motor complications. Interestingly, the mean plasma levodopa concentration and AUC were significantly increased following levodopa infusion despite the observation that this treatment was associated with a dramatic reduction in both 'off' time and dyskinesia.

This plasma pharmacokinetic profile may be easier to replicate with oral dopaminergic strategies than the constant level that has previously been considered necessary to provide 'continuous dopaminergic stimulation' [36]. We postulate that the development of an oral levodopa treatment strategy that avoids low trough levels may simulate a levodopa infusion and reduce the risk of motor complications associated with standard oral levodopa formulations.

Optimising the pharmacokinetics of levodopa metabolism – the role of COMT inhibition to achieve more CDS

Pharmacokinetic studies have shown that as a consequence of its short half-life (1–1.5 h), levodopa is rapidly metabolised in the periphery to dopamine before it reaches the brain [15, 21]. To overcome this pharmacokinetic limitation, levodopa is traditionally co-administered with a DDCI that inhibits one of the two main pathways responsible for its breakdown, such as carbidopa.

A number of strategies have been employed in the clinic to improve the delivery of oral levodopa/DDCI [22, 70] with the aim of providing less pulsatile and more continuous dopaminergic stimulation. Strategies have included shortening the intervals between each dose of levodopa, raising the total daily dose of levodopa, and changing the levodopa formulation [e. g., to controlled release (CR) levodopa]. However, none of these approaches have provided the complete control of parkinsonian symptoms. Also, as observed with the infusion technique of delivering therapeutic agents, these delivery methods have also proven to be inconvenient and difficult to manage. For example, frequent dosing regimens increase the possibility of missing a dose [68], and continually increasing the size of the levodopa dose generally leads to increased severity of dyskinesia. In addition, several clinical trials have shown conflicting

results with respect to the benefit observed following the use of CR preparations; some trials have shown a significant clinical benefit, whereas others have shown none (mainly attributed to the erratic absorption of the preparation effecting its bioavailability) [19, 20, 46, 72]. Because of this, CR tablets are generally only used either in combination with standard levodopa preparations or at night.

The second major pathway involved in the peripheral metabolism of levodopa is that provided by the action of COMT. Entacapone is a potent, selective, reversible, and peripherally-acting COMT inhibitor [35, 37, 57]. Having a similar pharmacokinetic profile to levodopa [51], entacapone can be easily co-administered in combination with traditional levodopa therapies in the clinic. Indeed, when levodopa is delivered in this manner (and in the presence of carbidopa), the net result is that the bioavailability of levodopa is increased [37]. This stems from the fact that the addition of entacapone extends the half-life of levodopa by approximately 85 % (from 1.3 to 2.4 h) leading to an increase (35–40 %) in the plasma levodopa area under the curve (AUC) [17, 37, 57].

The addition of entacapone to traditional levodopa/DDCI formulations therefore ensures that the maximum amount of levodopa reaches the brain from each single dose of levodopa administered in a smoother less pulsatile manner. This has implications for the time to emergence of levodopa-induced motor complications, if pulsatile dopaminergic stimulation is the underlying cause of their occurrence.

Levodopa dosing strategies to achieve more CDS and improve clinical outcome

Since the introduction of levodopa for the treatment of PD, most physicians have traditionally administered levodopa according to a widely accepted, three times a day dosing schedule. However, data gathered from pharmacokinetic studies have shown that this dosing strategy may provide pulsatile dopaminergic stimulation leading eventually to the onset of dyskinesia. Clinical trials are currently underway to determine a dosing strategy that provides less pulsatile and more CDS, whilst at the same time ensuring the levodopa concentration remains above a 'threshold' avoid trough levels and to prevent wearing-off (Fig. 1). Collectively, results emerging from these trials are correlating the link between levodopa dosing strategies, levodopa delivery and improvements in clinical benefit [64, 65].

Using the results from the levodopa dosing trials, a controlled prospective study (STRIDE-PD) is ongoing to test whether the administration of four doses of levodopa per day given at 3.5 hourly interval combined with entacapone may delay the appearance of dyskinesia compared to standard levodopa preparation. The results of this study will provide fundamental information about the correct use of levodopa in the early stage of the disease.

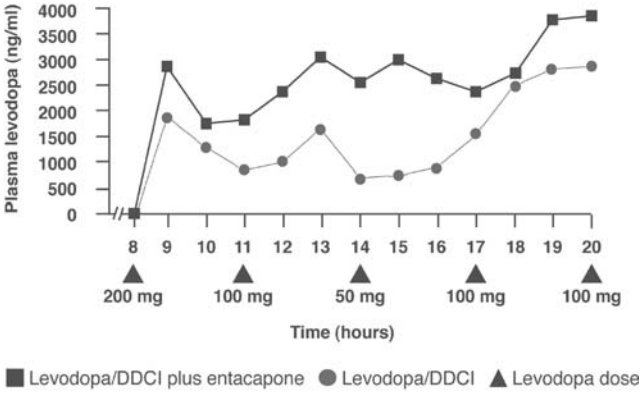

Fig. 1 Levodopa plasma levels after administration of levodopa alone or levodopa combined with entacapone given at 3-hourly intervals [66]

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