**Novel levodopa formulations in the treatment of Parkinson’s disease**

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Novel levodopa formulations in the treatment of Parkinson’s disease

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Abstract
Levodopa is the gold standard in Parkinson disease (PD) treatment but its use is associated with motor complications. Levodopa pharmacokinetics, its short half-life, erratic gastric emptying and duodenal absorption, are key factors in their pathogenesis. As disease progresses, frequency of levodopa administrations is increased leading to complex treatment schedules and poor patients’ compliance. The development of long acting formulations ensuring continuous delivery is therefore crucial to improve daily motor control. Available controlled release levodopa formulations produce more sustained plasma levels but show also lower bioavailability and slower time to peak, resulting in poor clinical outcome especially in advanced patients. IPX066 is a newly developed experimental formulation with more favorable plasma profile than immediate-release levodopa, resulting in improved motor control and reduced dose frequency, which may increase adherence. Novel delivery systems such as inhaled levodopa or transdermal levodopa micropumps are also currently investigated in their efficacy with promising future perspectives.

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Introduction
Parkinson's disease is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra leading to the reduction of endogenous dopamine [1].
Symptomatic therapy is based on dopamine replacement through administration of exogenous dopaminergic agents, such as levodopa (LD) and dopamine agonists (DA) [2]. LD is currently considered the most effective medication for PD [3]. Several studies comparing the effect of LD and DA showed that LD provides better symptomatic effect on motor symptoms [4-8]. Indeed, most PD patients initially treated with DA monotherapy, must be successively started on LD, to ensure satisfactory symptomatic control [9-11]. In the early stages, LD provides stable relief of parkinsonian symptoms and is well tolerated [3] and dyskinesias [12]. Recent studies showed that within 2-5 year of LD treatment more than 50% of patients develop motor fluctuations, while the risk of dyskinesia increases by 10% per year [4]. Although the mechanisms leading to the onset of chronic LD-related complications are not fully understood, converging evidence suggests that the onset of motor complications is related to its pharmacokinetics [14-17], as well as to the progression of the neurodegenerative process underlying PD [18]. Indeed it is suggested that continuous dopaminergic delivery may delay appearance of fluctuations and reverse motor complications once they have appeared, mainly by widening the therapeutic window [14]. The aim of the present review is to illustrate the rational for continuous dopaminergic stimulation and browse currently available and experimental pharmacological strategies aimed at improving LD delivery.
Etiopathogenetic mechanisms of motor complications and rational for continuous dopaminergic delivery
LD has short half-life ranging from 36 to 96 minutes [16], which leads to variable plasma levels, inconstant therapeutic effect and motor fluctuations [19]. Moreover, other pharmacokinetic factors may reduce drug availability at plasma and brain level, resulting in unsteady symptomatic control.
After oral intake, LD is absorbed in the duodenum and actively transported across the blood brain barrier (BBB) [20]. Reduced duodenal absorption and competition with dietary aminoacids may limit plasma bioavailability. Besides, plasma aminoacids may also reduce LD transit across BBB [20].
Finally, to exert its therapeutic effect, LD must be converted into dopamine, through decarboxylation. This process is carried out by specific enzymes called aromatic amino acid decarboxylase (AADC), which are present both in brain and in peripheral nervous system [21]. Peripheral decarboxylation of LD results in low brain bioavailability and in an increase of dopamine-related peripheral adverse events, such as nausea, vomiting and hypotension. Co-administration of LD and peripheral AADCI prevents peripheral dissipation of LD as well as side effects induced by the increase of dopamine [21]. Currently, all marketed LD compounds consist in combination with AADCI, namely carbidopa or benserazide.
Although motor fluctuations may occur in the early PD stages, they become more frequent and severe in advanced patients, indicating that disease progression and the underlying neuronal degeneration play a crucial role in their pathogenesis [18]. In the early stages, surviving nigrostriatal terminals preserve the ability to store and progressively release dopamine produced from exogenous LD. This mechanism ensures steady synaptic levels of dopamine and stable control of PD symptoms, despite fluctuations of plasma level.
These compensatory mechanisms are lost with progressive nigrostriatal degeneration and dopamine striatal nerve terminal decline. In the advanced phases, variations of plasma LD concentrations produce parallel swings in synaptic dopamine levels, resulting in fluctuating mobility [21].

Pulsatile dopaminergic stimulation not only results in unsteady control of motor symptoms, but also contributes to the onset of dyskinesias [22-27]. Animal studies showed that short acting drugs increase the risk of dyskinesias, while sustained dopamine receptor stimulation prevents their development [26].

Clinical evidences seem to confirm these findings. For instance, extended release dopamine agonists are less likely to induce motor complications, compared with standard release LD formulations [12]. Moreover, continuous delivery of dopaminergic drugs through subcutaneous infusion of apomorphine or intraduodenal LD reduces motor complications in advanced PD [27].

Summarizing, motor complications are closely linked to the short-acting effect of LD and with its pulsatile stimulation of dopamine receptors. Hence, the development of long acting formulations, able to ensure continuous dopaminergic delivery is crucial in order to provide steadier motor control throughout the day and prevent the mechanisms leading to the onset of dyskinesias and wearing-off [23-26].

**Available strategies to improve levodopa delivery**

Controlled-release (CR) carbidopa/levodopa preparations are provided with an erodible polymer matrix that retards LD release. CR formulations produce more sustained plasma levels than standard levodopa /carbidopa, but show lower bioavailability (71% vs 99%), slower time to peak concentration (2.3 versus 1.1 hrs), and delayed onset of clinical response (2.2 versus 1.1 hrs) [28].

Compared with standard release, CR formulations provided similar clinical benefit, with lower dosing frequency. On the other hand, patients treated with CR needed higher total daily dosage than standard formulations to achieve an adequate control of motor symptoms [29].

Levodopa /benserazide controlled release formulations are based on 'hydrodynamically balanced system' (HBS): the capsules are provided with a gelatine shell, which is slowly dissolved when in contact with gastric fluid. Once reached the stomach the capsules form a mucous body remaining in the stomach for a prolonged period of time and releasing the drug at a steady rate [30].

Compared with the standard LD, HBS formulations provide greater area under the concentration-time plasma curve, but have a longer delay in reaching peak concentration, which is paralleled by delayed symptomatic effect [31].

Levodopa methylester (ME) is a highly soluble prodrug produced by esterification of the carboxylic moiety of the LD molecule. This formulation provides more rapid and consistent absorption and therefore, more rapid onset of action vs. standard oral LD preparations, while the half-life of the two preparations is similar [33].

In a randomized trial, comparing the effectiveness of ME with standard LD in 221 patients with advanced PD, MLC produced a reduction of time spent in OFF condition, while standard LD did not. Nevertheless the difference of total daily OFF time between the two groups was not statistically significant [34].

A potential strategy to extend LD availability is inhibition of the enzymes involved in its degradation. Two additional major enzyme systems are involved in LD metabolic pathways: catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) [35, 36].
Entacapone, a peripheral COMT inhibitor, increases LD half-life by 25–50% without increasing peak concentration [37].

Tolcapone is a longer acting and more potent COMT inhibitor than entacapone which also exerts COMT inhibition in the brain [38-40]. In a study comparing 14 patients treated with tolcapone vs 11 patients treated with entacapone (n = 11), tolcapone was associated with greater reduction in duration of ‘off’ periods (1 hour vs 0.27 hour), and LD dose requirement [41].

Rasagiline provides irreversible and selective MAO-B inhibition, reducing the breakdown of dopamine and extending the action of endogenous and LD-derived dopamine in the brain[42,43]. Rasagiline is beneficial in treating motor symptoms in PD as monotherapy [44] and in combination with LD [45,46].

The LARGO (Lasting effect in Adjunct therapy with Rasagilne Given Once daily) study compared the effect of rasagilne and entacapone as add on to LD in patients with PD and motor fluctuations, showing that both drugs reduced mean daily off-time (-1.18 h rasagilne and -1.2 h entacapone) and increased daily on-time without troublesome dyskinesia [46].

Intraduodenal infusion of LD and carbidopa gel formulation, branded as duodopa, and subcutaneous infusion of apomorphine are currently indicated for the treatment of advanced PD [47-50]. Duodopa is administered through a portable pump directly connected with a tube located into the duodenum via percutaneous endoscopic gastrostomy [47,48].

Direct duodenal delivery ensures quick absorption of LD avoiding the variability of the absorption rate related to slow and erratic gastric emptying, such that continuous intraduodenal administration produces smaller variation in plasma concentration, compared with intermittent oral administration to the fact that it is given by in which the on the absorption rate. This treatment is effective in reducing the percentage of off time and in diminishing the on periods with disabling dyskinesia [48].

Apopomorphine is a short acting dopamine agonist. Subcutaneous continuous infusion of this drug through a programmable delivery system and a subcutaneous needle provides stable control of motor symptoms even in advanced PD [49], but achieves inconstant results on dyskinesias [50].

Such treatments are limited mainly by difficulties in the management of the infusion devises and by local adverse events at the site of infusion, which may even cause treatment discontinuation [51,52].

The most common and disabling side effects are subcutaneous nodules in the case of apomorphine [52], as well as intestinal problems related to percutaneous gastrostomy in the case of intraduodenal LD. Moreover the possible onset of neuropathy during treatment with intraduodenal LD has been reported although this maybe related to decreased vitamin B6 and B12 [48].

Intravenous infusion has also been tested for both LD and apomorphine. Intravenous infusion of LD results in stable plasma concentrations and improves motor fluctuations. However, it cannot be maintained for longer than 10-15 days due to the development of blood clots at the infusion site. Moreover, given the LD low hydrosolubility, high volumes of normal saline (250 ml for 200 mg of LD) are needed [53].

Melevodopa, which shows high solubility in water preparations, was also tested for intravenous infusion resulting in marked reductions of both plasma LD variations and motor response fluctuations in patients with either wearing-off or on-off phenomena. Unfortunately this treatment is complicated from peripheral vein phlebitis [54].
Intravenous route was also tested for apomorphine in an open label study. Five patients were switched from subcutaneous to intravenous apomorphine infusion and followed up for 7 months. Intravenous administration provided more stable plasmatic concentrations and less dyskinesias than subcutaneous infusion. On the other hand this treatment was complicated by life threatening adverse events, with three patients showing intravascular thrombotic complications requiring cardiothoracic surgery [55].

*Experimental formulations aimed at improving levodopa delivery*

IPX066 is an oral, extended-release capsule formulation of carbidopa-levodopa, developed to ensure more stable than immediate release LD plasma levels and to improve motor control of PD. IPX066 is not marketed, but clinical studies provided promising results [56].

Compared to standard release levodopa/carbidopa IPX066 showed similar Tmax (Time to maximum concentration) but greater area under curve. Administration of IPX066 every 6 hours (3.5 administrations/day) provided relatively stable plasma concentrations. Compared with standard levodopa/carbidopa IPX066 provided 87% higher exposure with modest increase in peak concentration [57].

A double-blind trial including 393 fluctuating PD patients compared the pharmacokinetics and clinical effect of standard LD and IPX066. After a first phase consisting in optimization of LD regimen to obtain the best therapeutic effect, patients were successively randomly allocated to receive optimized treatment with standard LD or IPX066. The mean daily dose of IPX066 was 1621.7 mg for all randomized subjects, while the mean daily LD dose for IR CD-LD after optimization was 814.5 mg.

Compared to immediate-release LD, IPX 066 provided a greater reduction of off-time, greater increase in “on-time” without troublesome dyskinesia, as recorded by diaries. Mean off time was about 6 hours in both groups at baseline, while residual off time at endpoint visit was about 5 hours in the LC group and 4 hours in IPX066. Significant improvements in Clinical Global impression and in “on-state” UPDRS Parts II and III were also observed in the IPX066 group. Moreover, IPX066 allowed reduction of dosing frequency with a mean number of administrations of 3.6 doses per day vs. 5 doses per day for the immediate release LD.

Prevalence of adverse events was similar in the two groups: the most frequent ones were sleep disorders, nausea, dizziness, dyskinesias diarrhoea, oedema peripheral, upper respiratory tract infection, urinary tract infection and sleep disorder [58].

Among the other investigational products, nebicapone is a promising molecule. It is a newly developed COMT inhibitor for the treatment of motor fluctuations [59], which has been tested in phase III clinical trials. Nebicapone is efficacious for the treatment of motor fluctuations in PD and significantly decreases the mean daily "Off" time compared to placebo and entacapone 200 mg (-81 min). However the observation that 4/200 exposed to this treatment presented increased liver transaminases is a matter of concern [60].

The synthesis of stereoselective drugs accessing cellular sugar transport systems is an interesting technical development to improve brain bioavailability of dopaminergic medications. One member of this new class is IPX-750, a stereoselective dopaminergic pro-drug designed to retain stereospecificity of binding at glucose transporters, dopamine transporter and dopaminergic receptors. In preclinical studies IPX 750 showed anti-Parkinson effects in three different PD rodent models, but no clinical trials with this molecule have been currently registered [61].
Other techniques to improve LD bioavailability are based on the use of microspheres or nano-particules, which improve peripheral and blood brain barrier absorption. Animal studies showed that levodopa/benserazide-loaded biodegradable microspheres or nanoparticles improve motor features and reduce the expression of dyskinesias in rats [62]. Alternative routes of administration, aimed at improve LD delivery, are also being explored in experimental studies. The transdermal route is currently used for DA rotigotine [63]. LD itself does not cross the normal skin, but treatment with cerulenin may increase skin permeation.

A single transdermal LD patch was formulated with calcium chloride and cerulenin dissolved in a propylene glycol:ethanol mixture. After a single topical application plasma concentration of LD was achieved within 3 h and maintained till 10 h. This formulation may be a noninvasive approach for continuous delivery of LD although there are issues related with the size of the patch and possible local skin reactions [64].

Trans-nasal and sublingual administration has been developed for different dopaminergic compounds [65] and for LD itself [66], but this route maybe suitable for intermittent and not for prolonged delivery.

Conclusions

Motor fluctuations and dyskinesias develop in the context of the progressive neurodegenerative process underlying PD [18]. On the other hand, there is no doubt that pharmacokinetics issues, particularly LD short half life and erratic gastric emptying and duodenal absorption, are key factors in the pathogenesis of motor fluctuations [17]. Moreover, pulsatile stimulation induces changes in pharmacodynamic post-synaptic receptor response contributing to the onset and worsening of motor complications [23]. Progressive increase of LD dose frequency partially prevents the variations of plasma drug levels and contrasts motor fluctuations, but often entails an increase of the total LD exposure, leading to worsening of dyskinesias [22]. Moreover, such treatment strategy results in complex treatment schedules, which may negatively affect patients’ compliance [67].

Other available oral strategies, such as adding COMT and MAO inhibitors, improve LD plasma profile and motor fluctuations, but are not sufficient to obtain a steady motor control through all the day [37-38] Moreover tolcapone may produce liver toxicity, which is not seen with entacapone, and is under strict regulations on liver enzyme monitoring [41].

The newly developed COMT inhibitor nebicapone was shown to significantly improve, as compared with entacapone and placebo. However, as well as tolcapone, it is associated with risk of increasing liver transaminases [60]. Further studies are being performed to verify the effectiveness and safety of this drug and results will be available shortly.

IPX066 is an experimental extended release LD formulation. Clinical studies showed that it has more favorable plasma profile than standard LD, resulting in a more stable motor control, without worsening of dyskinesias. Moreover IPX066 allows a reduction of the number of drug intake, which may positively influence patients’ compliance [58].

Differently from currently available controlled release formulations, IPX066 rapidly reaches plasmatic peak concentrations similar to immediate release LD [57], avoiding the delay or failure of clinical effect and drug failures observed with the "old" CR compounds [29].

IPX066 provided a significant reduction of about 2 h of off time, which is more than the reduction obtained with optimization of standard release LD therapy, which was paralleled by
a similar increase of on time with non-troublesome dyskinesias. On the other hand, at
endpoint, IPX066 treated patients still showed meaningful motor complications with a
considerable residual off time of about 4 hours (vs 5 hours in the standard LD group) and 1.5
hours of on time with troublesome dyskinesias [58]. These results suggest that IPX066 may
be a valid therapeutic option in PD patients with motor fluctuations and dyskinesias, but do
not achieve complete control of motor complications.

Further studies are warranted to verify whether IPX066 offers additional advantages
compared with already available therapies. This should also target the possibility that
improved treatment adherence, particularly in fluctuating PD patients, may minimize the risk
of excessive fragmentation and dosing, a potential risk factor for dyskinesia [67].

One study comparing pharmacokinetics, pharmacodynamics and clinical effect of IPX066 vs
levodopa/carbidopa/entacapone (www.clinicaltrials.gov-IPX066-B09-06) has been
completed, but its results are not yet available. Moreover it would be of great interest to
investigate whether the association of this new formulation with COMT and MAO inhibitors
is feasible and safe and offering further benefit in pharmacokinetic profile and clinical effect.
Alternative routes of administration are also increasingly used to improve dopaminergic
delivery. Intraduodenal infusion of LD provides stable plasmatic concentrations and steady
motor control, with parallel decrease of dyskinesias [47], but needs complex management
from both neurologist and gastroenterologist [51,52].

Several evidences indicate that continuous dopaminergic delivery may not only improve
motor fluctuations, but also prevent the mechanisms leading to their development and
progression. In the last years several studies have been carried out to compare the risk of
developing motor complications in patients treated with LD vs. patients treated with
dopamine agonists. Long-term follow-up of these studies is now available confirming that
patients initially treated with DA have a reduced the risk to develop motor complications,
even after add on of LD [5-8].

Conversely, the same studies showed that LD provides better symptomatic effect, and that
virtually all patients initially treated with DA need add-on of LD with the progression of the
disease to achieve satisfactory symptomatic control [9-12].

Moreover DAs are not suitable for all PD patients, as they are more prone than LD to
produce behavioral and psychiatric complications [68].

Providing a continuous delivery of LD, since the first stages of the disease may represent a
valid alternative to DA monotherapy as a starting therapy in early patients. Among oral
strategies, only controlled release LD formulations and the combination of entacapone and
standard LD have been studied in the early stages of the disease, but gave disappointing
results. Combined levodopa-entacapone therapy increased the risk for dyskinesias compared
to LD alone, maybe due to augmented exposure [69]. In a clinical trial comparing the
outcome at 5 years of levodopa/benserazide HBS vs. standard levodopa/benserazide in early
patients, there was no difference in the occurrence of motor fluctuations or dyskinesia [32].
Finally, IPX066 has been shown to be effective in advanced PD [58]. As this formulation
produces stable plasmatic curves, it may potentially prevent motor complications by
providing continuous delivery and receptor stimulation.

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