

Levodopa/carbidopa and entacapone in the treatment of Parkinson's disease: efficacy, safety and patient preference

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Abstract: Levodopa (LD) is the oldest, most efficacious and best-tolerated drug for dopaminergic substitution of patients with Parkinson's disease (PD). Its main drawback is its short half-life, which supports onset of motor complications in the long term. Therefore well-informed PD patients mostly accept LD therapy as late as possible. Recent LD trials indicate that a combination of LD with carbidopa (CD) and the catechol-O-methyltransferase (COMT) inhibitor entacapone (EN) may reduce the onset of these motor complications to a certain extent. This observation is further supported by pharmacokinetic trials and experimental research, but there is still a need to confirm this in a clinical trial, which is under way. Additionally, combined LD/CD/EN was superior to LD/CD administration regarding cognition, muscle behavior and gastrointestinal function in small clinical trials. Moreover there is accumulating evidence that combined COMT inhibition with LD administration reduces homocysteine synthesis. In the long term, homocysteine elevation supports onset of arteriosclerosis-related disorders, which are more frequent in PD patients according to epidemiological studies than in the normal healthy population. The introduction of LD/CD/EN in one tablet supported patients' preference of COMT inhibition as an essential component of LD/DDI therapy, as this combination reduced number and size of tablets.

Keywords: levodopa, entacapone, Parkinson's disease, preference, compliance, acceptance

Introduction

The oldest, most efficacious and best tolerated drug for dopaminergic substitution therapy of patients with Parkinson's disease (PD) is levodopa (LD).¹ Initially LD was administered as infusion, then in oral form.^{2,3} LD administration was improved by the addition of the dopadecarboxylase inhibitors (DDI), such as carbidopa (CD), which reduces the peripheral degradation of LD to dopamine. This therapeutic principle supports LD metabolism via the enzyme catechol-O-methyltransferase (COMT) and delivers more LD to the brain.

LD/DDI and COMT inhibition

A further development was the introduction of COMT inhibitors, which decrease peripheral LD degradation to 3-O-methyldopa (3-OMD) and thus further increase the delivery of LD to the brain.^{4,5} Two COMT-inhibitors, the only peripheral-acting entacapone (EN) and the additionally central-acting tolcapone,^{6,7} are currently marketed as adjuncts to LD/DDI application. Both prolong the half-life of LD in the periphery.

Important clinical trials on the efficacy of LD in PD patients

Out of the many investigations that demonstrated the efficacy of LD, the Earlier vs Later L-DOPA (ELLDOPA) trial was the first double blind trial, which compared the

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therapeutic efficacy of LD/CD in 3 different daily dosages of 150 mg, 300 mg or 600 mg with placebo treatment according to the guidelines of good clinical practice (GCP) in PD patients. This trial confirmed that LD is an efficacious and well tolerated compound. Interestingly, this study also provided some evidence for progression-modifying benefits of LD in PD patients despite its relative short duration of approximately 9 months. After a washout interval of 14 days, the three cohorts of LD-treated PD patients performed better than the ones with prior placebo treatment. There is some evidence from experimental and clinical outcomes that the peripheral dual inhibition of both LD-metabolizing enzymes increases the LD delivery to the brain compared to LD/CD.⁸ A further GCP trial on LD/CD efficacy, the FIRST-STEP (Favorability of Immediate-Release Levodopa/Carbidopa vs STalevo Short-Term comparison in Early Parkinson's disease) study, compared the efficacy of 2 different modes of LD application, the conventional LD/CD administration versus LD/CD with the COMT inhibitor EN.⁹ This trial additionally aimed to demonstrate that the currently available triple combination of LD/CD plus EN in 1 tablet (Stalevo®, Novartis) is safe in early PD patients with a need for LD therapy. This multicenter, double-blind, randomized, parallel-group study administered a fixed oral LD dose of 300 mg/day, distributed as 100 mg LD doses 3 times daily at 5-hour intervals to 424 PD patients. In this 39-week study, the PD patients in the LD/CD/EN arm performed significantly better than the ones in the LD/CD-treated cohort after week four throughout the remaining course of the study. This was found when the sum scores of the UPDRS part II (Activities of daily living) and UPDRS part III (motor examination) were compared as the main primary outcome at the remaining study visits. The statistical analysis was performed with the intention to treat population and employed the last observation carried forward procedure. The frequency of nausea and diarrhea was higher in the LD/CD/EN arm due to the additional COMT inhibition with particularly diarrhea as a common side-effect.⁹ Thus the FIRST-STEP trial confirmed the known additional LD/DDI efficacy-enhancing effects of EN, when given as extra tablet, to an existing LD/CD regimen in treated PD patients.¹⁰ However the design of the FIRST-STEP study lacked comparisons with placebo and treatment with dopamine agonists. One must realize that 300 mg LD/CD are not comparable to 300 mg LD/CD/EN, since the additional COMT inhibition with EN delivers more LD to the brain and thus improves the clinical efficacy of LD.

However both studies, FIRST-STEP and ELLDOPA, provide also some interesting findings about the onset and

frequency of fluctuating disturbances of motor behavior, the so called motor complications, in PD patients. These symptoms are a serious drawback of LD therapy, and induce a lot of concern in PD patients and their caregivers and considerably limit the acceptance of this compound.

Limitations of LD/DDI administration

There is a debate around mainly the clinical observation of the onset of fluctuations of movement in the course of PD following the so called "honeymoon period" of LD therapy. Motor complications are predominantly associated with LD/DDI due to the short half-life of LD. They are looked upon as one essential clinical marker for the progression of PD. Peaks and troughs of plasma levels of LD and thus correspondingly central striatal dopamine concentrations support occurrence of these initially predictable (which means dependent on previous PD drug intake) and later unpredictable (independent of previous PD drug application) fluctuations of movement. Clinically, they appear as involuntary motion sequences, the so-called dyskinesia, in the "ON" state. In contrast, "OFF" phenomena are characterized as temporary onset of the cardinal motor symptoms, akinesia, rigidity and tremor. They may indicate the decreasing efficacy of the last dopaminergic drug intake before the next one. Then they are characterized as wearing-off phenomena.

Both kinds of motor complications are combined with appearance of a wide array of non-motor symptoms.^{1,11-13} Various central-related hypotheses exist on the origin of these LD-associated motor complications. Loss of presynaptic dopaminergic autoreceptor function with resulting non-physiologic high synaptic dopamine concentrations and consecutive altered postsynaptic dopamine receptor activation and further downstream intracellular changes currently is one of the most widely accepted hypotheses. There is accumulating evidence that continuous nigrostriatal postsynaptic dopaminergic receptor stimulation may prevent onset of motor complications.¹⁴

COMT inhibition and onset of motor complications

Additional COMT inhibition with LD/DDI application is also suspected of preventing motor complications since the rise and fall of LD and also accordingly of striatal dopamine are less intense during COMT inhibition, ie, with EN. This supports the concept of continuous dopaminergic stimulation due to a less fluctuating delivery of LD to the brain.^{11,13-16} Thus threshold problems of dopamine are reduced at striatal

postsynaptic dopamine uptake sites. Therefore the frequency with which these receptors change between OFF and ON decreases.^{17–19} Accordingly, animal trials showed lower frequency and less intensity of manifestation of LD-associated motor complications in the long term, when a treatment with LD/DDI with the COMT inhibitor EN, given 4 times daily, was started right from the beginning.¹⁸ Further components for response variability to additional COMT inhibition and treatment of motor complications may be genetic features of the various COMT haplotypes. But no study has shown a clinical effect of the gene variations on the onset of motor complications and on the clinical efficacy of LD.^{20,21}

Onset of motor complications in the light of the FIRST-STEP and the ELLDOPA study

There is also some circumstantial evidence from the FIRST-STEP and ELLDOPA study that COMT inhibition with EN also reduces the frequency of motor complications. The ELLDOPA study showed that the higher was the daily administered LD dose, the more frequent were motor complications. In this trial, the occurrence of motor complications were at the placebo level in the 150 mg daily LD dose-treated cohort. However, onset of motor complications rose up to 3-fold in the 600 mg daily dose-treated group compared with placebo-treated PD patients (Table 1). In the FIRST-STEP trial, the number of monitored motor complications was higher in the LD/CD-treated arm in comparison with the LD/CD/EN-treated PD cohort. It is known that less LD reaches the brain during LD/CD administration in comparison with LD/CD/EN administration. Therefore onset of motor complications cannot be attributed to the LD compound itself as initially thought in discussions on the neurotoxicity of LD. This observation suggests that the application mode is essential for the onset of motor complications. However the number of noted wearing-off phenomena and dyskinesia was rather low in relation to the size of the study cohort and the short observation interval (Table 2).⁹ A further confirmatory result may be provided by the outcomes of the ongoing STRIDE-PD study. This trial aims to demonstrate that

Table 1 Frequency of motor complications in the ELLDOPA trial (%)

	LD/CD	LD/CD	LD/CD	placebo
	150 mg	300 mg	600 mg	
Dyskinesia	3.3	2.3	16.5	3.3
Wearing off	16.3	18.2	29.7	13.3

Table 2 Rate of motor complications in the FIRST-STEP trial (%)

	LD/CD/EN	LD/CD	Total	
Dyskinesia	2.7	4.2	3.5	week 39
Wearing off	8.8	12.0	10.4	week 39
Dyskinesia	5.3	7.4	6.4	at any study visit
Wearing off	13.9	20	17	at any study visit

LD/CD/EN, when used as initial LD therapy, significantly delays the time to onset of dyskinesia compared with the conventional LD/CD formulation. Nevertheless the optimum approach for LD therapy in view of the concept of continuous dopaminergic stimulation is the LD patch, which failed probably due to an insufficient design or side-effects, and the jejunal LD infusion. However this latter technique is expensive, complex and needs constant caregiver supervision. Further improvement is still required, which is under way. But it is an efficacious therapeutic option for treatment of motor complications in advanced PD patients.¹⁶ Therefore a further improvement of oral drug delivery is one of the essential goals for LD/DDI therapy, as, to a considerable extent, LD efficacy also depends on peripheral absorption and degradation mechanisms of LD.

Components that influence peripheral LD bioavailability

Plasma bioavailability of LD is influenced by body weight, previous LD intake in a chronic fashion and by gastric emptying of the LD tablet to the duodenal and jejunal tract, where LD absorption takes place.^{22–25} But PD patients often receive a drug combination therapy that involves multiple daily dosing of a particular compound and additional supplementation with other drugs at least partially sharing the modes of action. Efficacy of all administered compounds depends on patient compliance, the nature of the delivery system, physicochemical properties of the drug and physiological considerations. All of these are interrelated and affect the rate at which the drug is absorbed throughout the gastrointestinal tract and thus its bioavailability and pharmacokinetic profile.²⁶ In this respect EN improves the properties and dose of LD/DDI by prolonging the half-life of LD. But COMT inhibition may also promote the synthesis of more basic LD metabolites, ie, the tyrosine aminotransferase-dependent substrates dihydroxyphenylpyruvate acetate and trihydroxyphenylacetate. Therefore COMT inhibition may model the environmental pH and the physicochemical properties of LD for its duodenal absorption. COMT is located in higher concentrations in the membranes of the

gastrointestinal tract.^{26–30} Generally, these physicochemical properties of a drug also affect its absorption through the gastrointestinal tract.^{26,31} Compounds including LD are weak bases or weak acids or are the salts of these, and as such demonstrate pH-dependent solubility. The pH partition hypothesis asserts that the passage rate of a drug through a membrane is dependent on the environmental pH and pKa of the drug. Drugs with low pKa are not ionized in the stomach and subsequently rapidly absorbed. On passage to the small intestine with comparatively increased pH, the rate of ionization is changed and absorption subsequently slowed. The converse is true for drugs with higher pKa value. This influences the bioavailability of hydrophilic drug formulations. They have a narrow window of absorption, limited predominantly to the stomach or the upper intestine. Absorption is also limited by low pKa value and/or the site of active transport absorption mechanism, as in the case of LD.^{26,31,32} Additionally, absorption behavior of orally administered LD also depends on gastrointestinal transit rates, since uptake of LD occurs mainly in the proximal third of the small intestine (duodenum/jejunum) but not in the stomach. Intestinal LD absorption is rapid and complete, but the plasma bioavailability of LD is only 30% as a result of prior degradation to dopamine by DDI and to a lesser extent to 3-OMD by COMT, ie, in the gut membranes. The longer LD is retained in the stomach and in the small intestine the more extensively it is metabolized and made less available for absorption.²⁵ A formulation that shares the peripheral absorption site profile of LD, is sodium-octanoate, which is employed as [¹³C] marked substrate in breath tests. These investigations are a non-invasive, feasible, alternative method without ionizing radiation to measure gastric emptying of solids and liquids. After intake, [¹³C]-sodium-octanoate is rapidly absorbed from the proximal intestine and carried to the liver via the portal venous system. There it is oxidized and eliminated as CO₂ in the breath, reflecting gastric emptying as the rate-limiting step of the process. Accordingly, significant associations between pharmacokinetic plasma behavior of LD and the outcomes of the [¹³C]-octanoic acid breath test (OBT) appeared. In this study no impact of EN addition on gastric emptying time was found. But COMT inhibition with EN increased the recovery rate of the salt [¹³C]-sodium-octanoate.^{25,29,30}

The anti-acid scenario of COMT inhibition

It is known that medicaments are better absorbed with a rise in pH due to the dramatically improved solubility.

This results in a complete dissolution of the substance, which makes it readily available for absorption.^{26,32} Conventional LD/DDI is mainly metabolized to derivatives which lower the pH value. The main substrate is vanillic acid. This is formed from the initial tyrosine aminotransferase-dependent derivative dihydroxyphenylpyruvate followed by a COMT-dependent second metabolic step. An alternative pathway for the formation of vanillic acid is the COMT-triggered degradation of LD to 3-OMD with a subsequent tyrosine aminotransferase-dependent second step. A further metabolite is homovanillic acid, since this depends on the initial DDI-dependent conversion to dopamine. However this LD derivative may play a minor role, since a DDI is mostly applied nowadays with LD. Dopamine is metabolized to the initial MAO-dependent dihydroxyphenylacetic acid or as an alternative to the COMT-dependent 3-methoxytyramine. Both dihydroxyphenylacetic acid via COMT and 3-methoxytyramine via monoaminooxidases are then transformed to homovanillic acid. During LD/CD/EN administration, LD is mainly degraded to the tyrosine aminotransferase-dependent substrates dihydroxyphenylpyruvate acetate and trihydroxyphenylacetate and to a distinctly lesser extent to dihydroxyphenylacetic acid in the periphery.³³ This more basic milieu may hypothetically influence the activity of the intestinal H⁺-coupled nutrient, micronutrient and drug transporters in the mammalian small intestine and thus enable a better transport of acids into the peripheral blood circulation.^{26,31,32} Previous studies showed no effect of acute COMT inhibition with EN on gastric emptying. But these investigations did not exclude the possibility that repeat application of EN may influence the gastric emptying rate and further increase the bioavailability of co-administered substances.^{24,25,34} With LD, this may cause a deteriorated degradation and result in higher LD concentrations in the gastrointestinal membranes due to the simultaneous blocking of COMT by EN and DDI by CD. Since LD itself may contribute to delayed gastric emptying rate, this may result in the observed smoother increase of LD concentrations after repeat EN application. But these investigations support the conclusion that COMT inhibition combined with LD/DDI does not alter absorption of co-administered salts probably due to COMT inhibition-induced basic environment in gastrointestinal membranes. This improves dissolution and absorption of acids and salts and may therefore enhance the absorption and efficacy of LD.^{24,25,34} It will remain speculative whether this more basic scenario may also contribute to a better patient acceptance due to a lower incidence of gastrointestinal disturbances,

such as pyrosis. However it may also influence function of muscles.

COMT inhibition and muscle function

LD/CD application increases grip strength after standardized application and thus increases muscular strength in PD patients. LD/CD intake counteracts muscle weakness and thus indirectly also improves grip forces during both lifting and holding of a subject in an instrumental grip force paradigm in PD patients.³⁵ This may result from LD/CD-induced improvement of bradykinesia and rigidity. But referring to the impact of LD/CD on grip force, 150 mg LD/CD/EN was superior to the 200 mg slow release LD/CD formulation. Both LD formulations exhibited similar plasma pharmacokinetics of LD and clinical efficacy in terms of improvement of motor symptoms after standardized one time application. The LD/CD/EN-associated anti-acid scenario after LD/CD/EN intake may contribute to more basic pH values in skeletal muscles.^{25,33–36} This may support muscle function, since generation of acidic H⁺ ions, which are commonly attributed to the formation of organic acids such as primarily lactic acid, is buffered. As a result muscle excitability and contractibility improves. Both could have contributed to the observed augmented grip strength after LD/CD/EN intake in comparison with LD/CD administration.^{25,34–36} This trial underlined the importance of COMT inhibition in addition to LD/CD administration in PD patients beyond the impact of LD/CD on motor symptoms. A further important issue is the role of the 3-OMD, when LD/DDI is given with and without COMT inhibition.

COMT inhibition and 3-OMD metabolism

COMT inhibition reduces 3-OMD plasma concentrations. This could have influenced the attention-related components of an instrumental task performance, the line tracing test. In this trial, 150 mg LD/CD/EN was superior to 200 mg slow release LD/CD after standardized one time administration. There was no rise of 3-OMD during the LD/CD/EN administration but there was after LD/CD intake.³⁶ Therefore more LD was delivered to the brain during LD/CD/EN administration, since 3-OMD competes with LD during transport over the blood–brain barrier. Thus 3-OMD may interfere with the LD response by inhibiting tyrosine uptake in the striatum and subsequent LD utilization, which inhibits metabolism of LD to dopamine.^{37,38} It is known that small changes in catecholamine modulation of prefrontal cortex cells can

have profound effects on the ability of the prefrontal cortex to guide behavior.³⁹ Therefore this small difference of LD delivery to the prefrontal cortex could have been responsible for the described significant difference in the attention-related components of the line tracing task in favor of the LD/CD/EN condition. In contrast, the basal ganglia may better tolerate and compensate fluctuations of dopamine levels. However there are further metabolic aspects associated with a decreased 3-OMD synthesis, which is associated with homocysteine synthesis.

LD/DDI formulations, 3-OMD and homocysteine

LD applied only with a DDI increases homocysteine in plasma.⁴⁰ This may support the onset of atherosclerosis-related disorders, which has been shown in PD patients by epidemiological studies.^{41,42} To date, this LD-related homocysteine elevation has been considered as a long-term side effect in terms of onset of clinical consequences, ie, increase of vascular disease-related thickening of the intima media complex, and elevated risk of more neuropsychiatric complications, ie, depression and deteriorated cognitive function, in PD patients in earlier studies.^{43–46} However the outcomes of more recent trials were only partially confirmatory.^{47,48} This may be due to a relative low number of participants, and design and duration of these studies. Moreover the vitamin B and folic acid status and variations of the distribution of the polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene may play a role in the various investigated cohorts. In particular, the homocysteine MTHFR T/T allele promotes elevated homocysteine levels.^{43,49,50} But one must clearly state that a relationship between homocysteine levels and deleterious consequences in PD, for instance stroke or cognitive decline, has not been conclusively demonstrated.

Therapy of homocysteine elevation with COMT inhibition

An approach for homocysteine decrease in plasma is application of COMT inhibitors as adjunct to LD/DDI formulations, as this combination reduces O-methylation of LD. Addition of the COMT inhibitor tolcapone to a stable antiparkinsonian drug regime reduced homocysteine plasma levels. This small prospective trial provided some evidence that COMT inhibition lowers homocysteine generation.⁵¹ In rats, this was also shown with the peripherally acting COMT inhibitor EN.⁵² Clinical data of EN in humans are still under discussion. There are prospective negative

studies, but they may have been under powered because of folate supplementation in the American and Canadian diet, leading to a milder increase in homocysteine than expected.^{44,53,54} Observational European non-prospective studies showed lower homocysteine levels in EN-treated patients.^{55–57}

Homocysteine metabolism in relation to peripheral and central COMT inhibition

These findings warrant a discussion about which COMT inhibitor, EN or tolcapone, is more suitable for modulating homocysteine synthesis. In contrast to the controversial results for EN acting only in the periphery, tolcapone even reduced homocysteine levels following repeated intake.⁵¹ This may indicate a certain superiority of tolcapone over EN in terms of impact on homocysteine metabolism. But it may also result from the different study designs used. However there is an essential pharmacological discrepancy between both compounds, since tolcapone but not EN also occurs and acts centrally.^{6,7} Thus tolcapone may even reduce homocysteine levels within the brain and thus the associated neurotoxic effects of homocysteine.^{58,59} Central COMT activation caused a sustained synthesis of homocysteine in astrocytes and transport of this amino acid to neurons. This was blocked by COMT inhibition, which was seen as neuroprotective. Moreover glial COMT reduced N-methylation of the dopamine derivative salsolinol to N-methylsalsolinol or of the tetrahydroisoquinolines (TIQ) to the corresponding neurotoxic N-methylisoquinolinium ions.^{60–62} Therefore central COMT inhibition may turn out to be a double-edged sword, since the broad detoxification potential of COMT within the brain is reduced. Thus exclusive central COMT inhibition may also force central dopamine degradation to metabolism via monoamine oxidase B, which generates oxidative stress. Therefore oxidative stress was found in combination with S-adenosylmethionine (SAM) depletion, as SAM is the methyl donor for nicotineamide N-methylation and most other important methylation reactions.^{7,61,63–66} Accordingly, reduced SAM levels were found in chronic neurodegeneration.^{67–70} LD/DDI further lowered SAM concentrations,⁷¹ as O-methylation of LD by COMT elevates homocysteine.^{58,64,72} Consequently, one may suggest combining central COMT inhibition with central blocking of monoamine oxidase-B. This may increase the generation of free radicals via monoamine oxidase A-induced dopamine degradation. Moreover this may further promote the shift from O-methylation to

N-methylation, and a cumulative metabolism of dopamine and other substrates via N-methylating enzymes. As a result, an increment of neurotoxic N-methylated TIQs synthesis may occur, as shown in clinical studies.^{73,74} Only LD/DDI-treated but not untreated PD patients showed increased levels of N-methylated TIQs, but not of their corresponding metabolic precursors.^{75–78} Thus in conclusion this increased risk of PD accelerating synthesis of free radicals and N-methylated TIQs associated with central COMT inhibition may suggest peripheral COMT inhibition as adjunct for LD/DDI therapy. This may also underline the safety of EN in the treatment of PD patients, which is one of the essentials for accepting the intake of a compound in the long term.

The safety of EN long-term application

Numerous trials and reviews have proven and reported the long-term tolerability and safety of EN treatment in PD patients. The introduction of the triple combination LD/CD/EN in one tablet is also safe and efficacious. Combined EN application with selegiline, dopamine agonists and antidepressants such as imipramine was well tolerated.^{79–89} Observed discoloration of the urine is harmless, but the patient should be informed before start of therapy by the treating physician. In contrast there was always a certain debate about putative peripheral and central toxic effects of tolcapone.⁶³ This was followed by reports that tolcapone causes onset of serious hepatic reactions with development of severe, sometimes fatal, hepatic disease as well as possible occurrence of rhabdomyolysis and neuroleptic malignant-like syndrome. One assumes that patients with mutations in the UDP-glucuronosyltransferase 1A9 gene, which leads to defective glucuronidation activity, may be predisposed to COMT inhibitor-induced hepatotoxicity.⁹⁰ Therefore tolcapone was temporarily withdrawn nearly all over the world. The most frequent non-dopaminergic adverse event of COMT inhibition was diarrhea, usually 2 to 4 months following treatment initiation. This may be due to the inhibition of 5-HT metabolism in the gastrointestinal tract, which causes an increase of gastrointestinal motility in some PD patients.^{4,5} Headache, increased sweating and associated xerostoma probably due to aggravation of dyskinesia in clinical trials, abdominal pain, and harmless urine discoloration are more frequently reported than in the placebo arm in clinical trials that tested the efficacy of COMT inhibitors. But the discussion on the liver toxicity of tolcapone with a demand for regular liver function tests also biased the patients' preference for

EN intake. An additional negative criterion for tolcapone use is the need for a previous failed response to EN or intolerance of intake of other COMT inhibitors.

Aspects of patient preference for LD/CD combined with EN intake

Treatment of PD often requires intake of an increasing number of tablets with progression of the disease, which results in compliance problems. Therefore discipline and education of patients and their caregivers are essential tools to minimize any behavior that might limit the efficacy of compounds.^{91,92} Advanced PD patients must often take LD doses more frequently (LD “fractionation”) and as continuously as possible, since fluctuations of plasma LD levels and accordingly motor performance should be reduced. In this regard the introduction of the triple combination LD/CD/EN in one tablet was an essential step forward in contrast to the older LD/DDI plus EN administration as an extra tablet. Now oral LD/CD/EN therapy requires intake of half the number of tablets. Moreover the pills of the LD/CD/EN formulation are distinctly smaller, which favors patients’ acceptance. A remaining drawback is the availability of this combination in only a few LD dosages, which limits the titration possibilities for the physician in comparison with LD/CD. This drawback should be remedied in the near future with the necessary introduction of 25 mg, 75 mg, 125 mg, 175 mg LD/CD/EN formulations. However for titration speed, efficacy and tolerability LD/CD/EN is superior to that of dopamine agonists, which still have the advantage of delaying the time to onset of motor complications, as proven by numerous studies and reviews.^{93,94} But one must realize that there is still a lack of data on patient preference and of comparative studies on other forms of LD, such as controlled-release formulations, on infusion application modes and on dopamine agonists.

Conclusion

Additional peripheral COMT inhibition with EN is an improvement on LD/DDI administration in PD patients. It contributes to a better cognition, muscle force and movement behavior performance according to clinical outcomes. There is some evidence that peripheral COMT inhibition also delays onset of motor complications and supports occurrence of lower homocysteine plasma levels, which, when elevated, represent a risk factor for accelerated PD progression and arteriosclerosis. The triple combination LD/CD/EN in one tablet is an essential step forward, since pill size and number of tablets taken are reduced. This formulation improved

patients’ acceptance and preference in addition to its proven better safety compared with tolcapone.

Disclosures

The author has no conflicts of interest to disclose.

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