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Review

Editor's comment: Levodopa has now been available for the treatment of Parkinson's disease for over 40 years and most neurologists are very familiar with its use. Familiarity may, however, lead to a somewhat cavalier attitude toward the potential problems that can be encountered with the use of levodopa. I suspect that very few neurologists, me included, have been acutely aware of the potential for levodopa to produce peripheral neuropathy and of the frequency with which it does so. In this review, Müller and colleagues provide a tremendously valuable service by bringing this to our attention and discussing approaches to treat and potentially avoid this surprisingly common and sometimes dangerous adverse effect of what is still the most effective treatment available for Parkinson's disease.

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Peripheral neuropathy in Parkinson's disease: Levodopa exposure and implications for duodenal delivery ***[Universally Available]***

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ABSTRACT

In advanced Parkinson's disease (PD) patients, continuous intra-duodenal infusion of levodopa/carbidopa intestinal gel (LCIG) is an established approach in the management of motor complications that cannot be further improved by conventional oral therapy. In general, tolerability of LCIG has resembled that of oral dopaminergic therapy; however, cases of symptomatic peripheral neuropathy (PN), sometimes severe, have been reported in patients receiving LCIG. Cases are generally a sensorimotor polyneuropathy with both subacute and chronic onsets, often associated with vitamin B12 and/or B6 deficiency. Rare cases clinically resemble Guillain-Barré syndrome. In the absence of prospectively collected data on possible associations between LCIG and PN, it is prudent to explore potential mechanisms that may explain a possible relationship. The PN may be linked to use of high-dose levodopa, promoting high levels of homocysteine and methylmalonic acid or reduced absorption of vitamins essential for homocysteine metabolism. Cases of LCIG-associated PN often have responded to vitamin supplementation without need for LCIG cessation, although LCIG cessation is sometimes necessary. It may be advisable to monitor vitamin B12/B6 status before and after patients start LCIG and be vigilant for signs of PN. Prospective, large-scale, long-term studies are needed to clarify whether vitamin supplementation and routine use of a catechol-*O*-methyltransferase inhibitor may help prevent PN in LCIG recipients and whether these measures should be routine practice in patients with PD on high-dose oral levodopa.

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1. Introduction

Half a century after its introduction, levodopa continues to be the most effective pharmacotherapeutic option for ameliorating the motor symptoms of Parkinson's disease (PD) [1,2]. In advanced PD with severe complications that cannot be controlled by oral or transdermal adjuncts to oral levodopa, invasive pharmacologic and surgical options have included the continuous subcutaneous infusion of the dopamine agonist apomorphine [3,4] and deep brain stimulation (DBS) of the bilateral subthalamic nucleus or internal globus pallidus [5–7]. Continuous intra-duodenal infusion of levodopa/carbidopa intestinal gel (LCIG), a carboxymethylcellulose (carmellose sodium) gel suspension of levodopa plus the dopa-decarboxylase inhibitor (DDI) carbidopa [8], is another recent continuous drug delivery approach for advanced PD.

Tolerability resembles that of oral dopaminergic therapy [9–12], except for surgical and delivery-system events (e.g. tube dislocation) [10,11,13]. LCIG uses a carboxymethylcellulose/water vehicle, an agent that is frequently used as a food thickener [14]. Cases of symptomatic peripheral neuropathy (PN)—some severe—have been reported in LCIG recipients [12,15,16]; however, overall incidence cannot be estimated from these case reports. PN also has been reported in long-term recipients of oral levodopa, in whom signs or symptoms develop in as many as 12% [17,18].

This review describes the reported cases, surveys the mechanisms hypothesized for subacute and chronic cases and offers interim suggestions for management and possible prevention.

2. Methods

A thorough and systematic literature search of PubMed used multiple combinations of the following search terms: "advanced Parkinson", "advanced Parkinson's disease", "levodopa", "duodenal levodopa infusion", "levodopa/carbidopa intestinal gel", "LCIG", "polyneuropathy", "peripheral neuropathy", "neuropathy", "vitamin B" and "homocysteine". We subsequently reviewed abstracts for relevance and then searched the reference lists of appropriate articles to obtain any other pertinent references or search terms that were not captured during the original PubMed search.

3. Results: review of the literature

3.1. PN in PD in the absence of LCIG therapy

PN occurs in patients with PD (Table 1). PN was identified clinically and by electromyography (EMG) in 10 (43%) of 23 patients

Table 1
PN and related findings in PD case series and other studies.

Authors/year	Type of study (patient groups)	PN prevalence	Clinical findings	Interventions/outcomes
Taly et al., 1992 [19]	Case series (29 juvenile-PD patients)	Abnormal sensory conduction in 31%; abnormal motor conduction in 14%	–	–
Khan et al., 2003 [20]	Genetic case series (24 patients with *parkin* mutation)	Symptomatic PN in 1 levodopa-naïve patient	Axonal PN	"Dramatically" responsive to trihexyphenidyl initially; moderate motor response at 7 years
Müller et al., 2004 [21]	Pharmacokinetic/pharmacodynamic (31 patients on oral levodopa/DDI; 27 non-PD controls)	–	Sural-nerve action potentials were lower in PD patients than in controls (in association with homocysteine elevation), but conduction velocity was no different	–
Ohsawa et al., 2005 [22]	Case–control study (9 PD patients with *parkin* mutation; 8 idiopathic PD patients)	Sensory symptoms in 2 *parkin*-mutation patients and 2 idiopathic PD patients	Reduced sural-nerve action-potential amplitude in 8 *parkin*-mutation patients but not in idiopathic PD patients	–
Nolano et al., 2008 [23]	Case–control study (18 PD patients; 30 healthy controls)	Paresthesia or "burning feet" in 33%	Across the PD group, abnormal sensation thresholds plus epidermal nerve-fiber and Meissner corpuscle loss	–
Toth et al., 2008 [17]	Case–control study (34 PD patients with symptomatic idiopathic PN; 22 PD-only patients; 258 non-PD PN patients)	All cases (by study design)	Elevated homocysteine or MMA	Intra-muscular B12 led to PN stabilization at 24 and 36 months
Chovancova et al., 2009 [24]	Case series (23 PD patients)	PN signs in 43%	–	–
Capuano et al., 2010 [12]	ADR-database search	PN in 7 patients on LCIG (among an undescribed number of ADR reports)	Neuropathy in 2, polyneuropathy in 3, GBS in 2	LCIG cessation or interruption led mostly to at least gradual improvement
Gondim et al., 2010 [25]	Case series (10 PD patients with PN)	All subjects (by study design)	Primarily axonal PN but demyelinating features in 2 patients; low B12 and/or elevated homocysteine in 6 patients; all patients on oral levodopa	Intra-muscular B12 and oral folate led to PN improvement (time frame not specified)
Montastruc et al., 2010 [26]	ADR-database search	PN in 3 patients on oral levodopa (among 174,341 ADR reports)	PN was reported as ADR, but levodopa role was excluded or doubtful	–
Toth et al., 2010 [18]	Case–control study (58 PD patients; 58 community controls)	PN signs in 55% of patients and 9% of controls; symptomatic PN in 41% of patients and 5% of controls	Predominantly axonal PN, associated with levodopa exposure; elevated homocysteine and MMA	–
Nolano et al., 2011 [27]	Case series (21 PD patients)	–	Meissner corpuscle loss found only in levodopa recipients	–
Rajabally et al., 2011 [28]	Cross-sectional, case–control study (37 PD patients and 37 controls)	PN in 38% of PD patients and 8% of controls	Associated B12 deficiency in 50% of patients with PD + PN and 14% of non-PD controls; significant correlation among cumulative levodopa exposure, B12 level and PD duration in patients with PD + PN	–

ADR = adverse drug reaction; DDI = dopa-decarboxylase inhibitor; GBS = Guillain-Barré syndrome; LCIG = levodopa/carbidopa intestinal gel; MMA = methylmalonic acid; PD = Parkinson's disease; PN = peripheral neuropathy.