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Clinical Study

Intraduodenal levodopa-carbidopa intestinal gel infusion improves both motor performance and quality of life in advanced Parkinson's disease

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ABSTRACT

We report the efficacy and adverse effect profile of intraduodenal levodopa-carbidopa intestinal gel (LCIG) infusion from patients treated in a single Australian movement disorder centre. We conducted an open-label, 12 month prospective study of treatment with LCIG in patients with advanced Parkinson's disease in a single tertiary referral hospital unit specialising in movement disorders. Patients with levodopa-responsive, advanced Parkinson's disease with motor fluctuations despite optimal pharmacological treatment were enrolled and underwent a 16 hour daily infusion of LCIG for 12 months. Fifteen participants completed the trial. The mean (±standard deviation) improvement in Unified Parkinson's Disease Rating Scale part III was 37 ± 11%, mean daily "off" period reduced from 6.3 ± 2 to 1.9 ± 2 hours, total daily "on" time increased from 10.2 ± 3 to 13.7 ± 2 hours, "on" period without dyskinesia increased from 4.5 ± 3 to 7.5 ± 5 hours, and 39-item Parkinson's Disease Questionnaire Summary Index score improved by 32.5 ± 35%. The most common adverse event was reversible peripheral neuropathy secondary to vitamin B12 ± B6 deficiency (40%), local tube problems (40%), and impulse control disorder (ICD) (27%). No patient had stoma bleeding or peritonitis. All patients with ICD had a past psychiatric diagnosis of depression with or without anxiety and a higher daily levodopa intake at 6 and 12 months of LCIG infusion. Intraduodenal LCIG improves motor performance, quality of life and daily "on" period. Prior to and during duodenal LCIG infusion, clinicians should monitor for peripheral neuropathy and vitamin B12 and B6 deficiency, as supplementation can reverse peripheral neuropathy. This trial is registered at Clinicaltrials.gov as CT00335153.

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1. Introduction

Most Parkinson's disease (PD) patients eventually develop motor fluctuations that become difficult to control, even with frequent dosing of levodopa [1]. A significant component of motor fluctuations is related to fluctuating levels of serum levodopa secondary to delayed gastric emptying and competition with amino acids for intestinal absorption [2,3]. Intraduodenal delivery of levodopa achieves relatively steady serum levodopa levels and provides a therapeutic option in patients with severe motor fluctuations [2]. Levodopa-carbidopa intestinal gel (LCIG) (Duodopa; AbbVie, Botany NSW, Australia) infusion is approved for clinical use in over 30 countries and has been used in over 2,800 patients worldwide [4]. We report, to our knowledge, the largest single centre experience in an Australian movement disorder unit using LCIG infusion.

2. Method

Data were collected prospectively from the first 15 consecutive patients treated with LCIG in the Movement Disorders Unit at Westmead Hospital. The first patient commenced treatment in March 2008. Four of the patients were treated compassionately via the Special Access Scheme and the remaining eleven treated through participation in an open-label, phase III, 12 month study of the safety and efficacy of LCIG in advanced PD, the full results of which have recently been published [5]. The following information was recorded at baseline: age, age at PD onset, sex, duration of PD (years), Minnesota Impulse Disorders Interview

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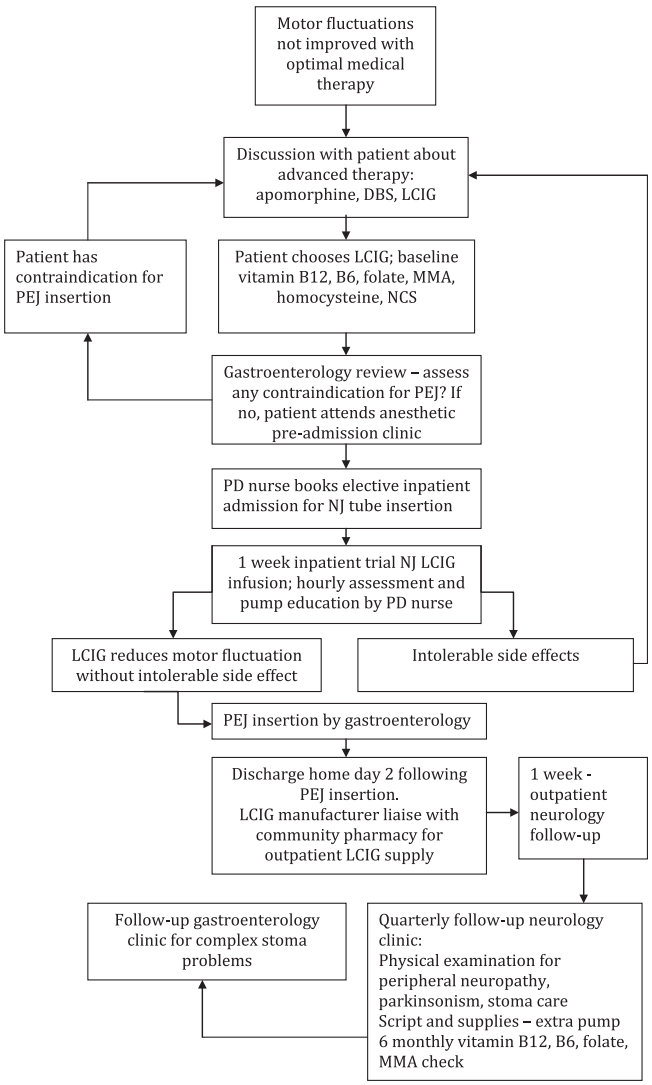

Fig. 1. Flowchart illustrating how intraduodenal levodopa-carbidopa intestinal gel infusion is set up and maintained in the hospital setting. DBS = deep brain stimulation, LCIG = levodopa-carbidopa intestinal gel, MMA = methylmalonic acid, NCS = nerve conduction study, NJ = nasojejunal, PD = Parkinson's disease, PEJ = percutaneous endoscopic jejunostomy.

(MIDI), medication list, the total levodopa daily equivalent dose, Unified Parkinson's Disease Rating Scale part III (UPDRS) 1 to 4 hours after the first usual parkinsonian medication, 39-item Parkinson's Disease Questionnaire (PDQ-39), daily hours "off", daily hours "on" without dyskinesia, daily total hours "on" and pre-existing psychiatric diagnosis or impulse control disorder (ICD). Following commencement of LCIG therapy, all dopamine agonists were ceased. LCIG was administered for up to 16 hours during the day, commencing on waking, and was turned off at night. The only treatment allowed for nocturnal "off" symptoms was immediate release oral levodopa/carbidopa. The doses of all antiparkinsonian medications at baseline were converted to equivalent levodopa daily dose using a standardised conversion table from the paper by Tomlinson et al. [6]. The total daily LCIG dose was calculated from the daily morning dose, total daily bolus dose plus the continuous dose per hour multiplied by total hours of infusion per day. The percentage change from baseline daily levodopa dose was compared to daily levodopa equivalent dose at 6 months. At 3, 6 and 12 months, the mean hours "off" per day, mean hours "on" per day without dyskinesia and mean total hours "on" (with or without dyskinesia) were obtained from the patient's self-reported diary over 3 days. The PDQ-39 and UPDRS while the patient is "on" from the usual anti-parkinsonian medication was recorded at 6 and 12 month follow-up. From March 2008 to July 2011, we recorded complications for all study participants. The complications assessed were death, stoma site infection, bleeding, percutaneous endoscopic gastrojejunal tube problems, number of additional radiographs, fluoroscopy and endoscopy required, and development of peripheral neuropathy. The study was approved by the Human Research Ethic Committee at Western Sydney Area Health Service and written consent was obtained from all subjects. The authors had full access to all of the data in the study (Fig. 1).

Results are reported as mean ± standard deviation unless otherwise stated.

3. Results

3.1. Patient demographics and baseline characteristics

Five women and ten men participated in this study. The mean age was 62 ± 4.74 years. The mean age at Parkinson's disease onset was 48 ± 11.15 years. The mean duration from onset of disease to requiring LCIG was 14 years. The patients' mean UPDRS part III (on usual PD medications) was 52 ± 23.9 prior to LCIG infusion. The mean daily oral levodopa dose prior to LCIG infusion was 2141 ± 940 mg. Thirteen out of 15 patient were taking dopamine agonists, either apomorphine, pramipexole and/or pergolide at baseline.

3.2. Treatment duration and levodopa dose

Following 6 months of LCIG infusion, 66% of patients had a reduction in total daily dose of levodopa by 28 ± 19.7% (from 2,540.0 ± 677.6 mg at baseline to 1,864.3 ± 701.3 mg per day). Thirty-three percent of patients had an increase in total daily dose of levodopa after 6 months of LCIG infusion. The mean 6 month increase in total daily levodopa dose in these patients was 19 ± 53.4%.

3.3. Discontinuations

LCIG was well tolerated and no patients discontinued LCIG due to its side effects. Five patients did not keep a daily diary at 3 months and this increased to seven patients at 6 months. No patient died during the study period.

3.4. Changes in UPDRS, hours "on" and "off" and PDQ-39

The mean improvement in part III of UPDRS was 31 ± 36% at 6 months and 37 ± 11% at 12 months. Patient mean daily "off" period reduced from 6.3 ± 2 hours to 1.9 ± 2 hours and this was maintained at 12 months. The total daily "on" period increased from

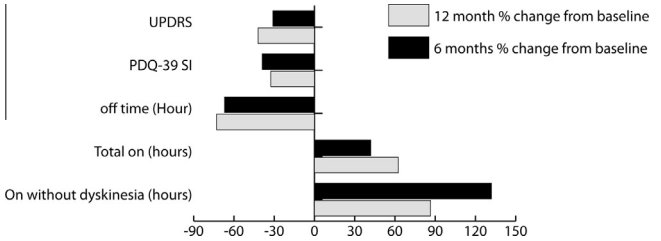

Fig. 2. Mean percentage change of Unified Parkinson's Disease Rating Scale daily "on", "off" hours and 39-item Parkinson's Disease Questionnaire Summary Index from baseline at 6 and 12 months. PDQ-39 SI = 39-item Parkinson's Disease Questionnaire Summary Index, UPDRS = Unified Parkinson's Disease Rating Scale.

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