Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study

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Summary

Background Levodopa is the most effective therapy for Parkinson's disease, but chronic treatment is associated with the development of potentially disabling motor complications. Experimental studies suggest that motor complications are due to non-physiological, intermittent administration of the drug, and can be reduced with continuous delivery. We aimed to assess efficacy and safety of levodopa-carbidopa intestinal gel delivered continuously through an intrajejunal percutaneous tube.

Methods In our 12-week, randomised, double-blind, double-dummy, double-titration trial, we enrolled adults (aged ≥30 years) with advanced Parkinson's disease and motor complications at 26 centres in Germany, New Zealand, and the USA. Eligible participants had jejunal placement of a percutaneous gastrojejunostomy tube, and were then randomly allocated (1:1) to treatment with immediate-release oral levodopa-carbidopa plus placebo intestinal gel infusion or levodopa-carbidopa intestinal gel infusion plus oral placebo. Randomisation was stratified by site, with a mixed block size of 2 or 4. The primary endpoint was change from baseline to final visit in motor off-time. We assessed change in motor on-time without troublesome dyskinesia as a prespecified key secondary outcome. We assessed efficacy in a full-analysis set of participants with data for baseline and at least one post-baseline assessment, and imputed missing data with the last observation carried forward approach. We assessed safety in randomly allocated patients who underwent the percutaneous gastrojejunostomy procedure. This study is registered with ClinicalTrials.gov, numbers NCT00660387 and NCT0357994.

Findings From baseline to 12 weeks in the full-analysis set, mean off-time decreased by 4·04 h (SE 0·65) for 35 patients allocated to the levodopa-carbidopa intestinal gel group compared with a decrease of 2·14 h (0·66) for 31 patients allocated to immediate-release oral levodopa-carbidopa (difference –1·91 h [95% CI –3·05 to –0·76]; p=0·0015). Mean on-time without troublesome dyskinesia increased by 4·11 h (SE 0·75) in the intestinal gel group and 2·24 h (0·76) in the immediate-release oral group (difference 1·86 [95% CI 0·56 to 3·17]; p=0·0059). In the safety analyses 35 (95%) of 37 patients allocated to the levodopa-carbidopa intestinal gel group had adverse events (five [14%] serious), as did 34 (100%) of 34 patients allocated to the immediate-release oral levodopa-carbidopa group (seven [21%] serious), mainly associated with the percutaneous gastrojejunostomy tube.

Interpretation Continuous delivery of levodopa-carbidopa with an intestinal gel offers a promising option for control of advanced Parkinson's disease with motor complications. Benefits noted with intestinal gel delivery were of a greater magnitude than were those obtained with medical therapies to date, and our study is, to our knowledge, the first demonstration of the benefit of continuous levodopa delivery in a double-blind controlled study.

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Introduction

Parkinson's disease is characterised by degeneration of dopamine neurons in the substantia nigra pars compacta with resultant depletion of striatal dopamine leading to the core motor features of the disease. The mainstay of treatment is levodopa, the aminoacid precursor of dopamine. Nearly all patients with Parkinson's disease have a beneficial response, and no present medical or surgical therapy has been shown in controlled trials to provide greater antiparkinsonian benefit. However, chronic oral levodopa therapy is associated with development of potentially disabling motor complications (motor fluctuations and dyskinesia) in most patients.[1] Motor fluctuations consist of an initial benefit after a dose of levodopa (on-time) followed by a return of parkinsonian features (off-time) before onset of benefit from the subsequent dose. Dyskinesias are involuntary movements induced by levodopa that typically occur during on-time. Raised doses of levodopa can reduce off-time but tend to increase dyskinesia, whereas a reduction in levodopa dose can reduce dyskinesia but tends to worsen off-time. In patients with advanced Parkinson's disease, provision of a dose of levodopa that satisfactorily controls off-time without inducing dyskinesia can be difficult. Several

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See Comment page 128

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classes of medication (eg, dopamine agonists, catechol-O-methyl transferase [COMT] inhibitors, and monoamine oxidase B [MAO-B] inhibitors) have been developed to try to reduce off-time, but these drugs typically provide only modest benefit and are frequently worsen dyskinesia.[2] Deep brain stimulation is widely used in advanced patients to improve off-time and rates of dyskinesia, but requires a neurosurgical intervention that is associated with potentially serious complications.[3,4] Development of a levodopa formulation that provides benefits without inducing or worsening motor complications is a major unmet need in Parkinson's disease.

Clinical and laboratory evidence suggests that levodopa-induced motor complications are related to the non-physiological restoration of brain dopamine with intermittent doses of standard oral levodopa.[5] Striatal dopamine concentrations are normally maintained at a fairly constant level. However, in Parkinson's disease, in which there is a loss of nigrostriatal terminals, striatal dopamine levels are dependent on the peripheral availability of levodopa. Intermittent dosing with standard oral levodopa formulations provides fluctuating plasma levels due to erratic gastric emptying, variable jejunal absorption, and the short half-life of the drug (60–90 min).[6,7] In the dopamine-depleted state, this variability in plasma concentrations of levodopa is translated into abnormal, fluctuating, striatal dopamine concentrations,[8,9] which in turn are associated with non-physiological intermittent or pulsatile stimulation of dopamine receptors. This intermittent stimulation results in gene and molecular changes in striatal neurons, neurophysiological changes in the firing pattern of pallidal output neurons, and the development of motor complications.[5]

Continuous delivery of levodopa might restore brain dopamine in a more physiological way, and thereby avoid or reduce motor complications associated with traditional levodopa therapy.[5,10] Continuous levodopa infusion has been reported to reduce both off-time and dyskinesia in open-label studies in patients with advanced Parkinson's disease.[11–13] However, development of oral or patch formulations that deliver levodopa in a continuous way has been problematic.

Levodopa-carbidopa intestinal gel (AbbVie, North Chicago, IL, USA) is a carboxymethylcellulose aqueous gel that can be delivered continuously to the proximal jejunum via a percutaneous gastrojejunostomy tube connected to a portable infusion pump (CADD-Legacy, Smiths Medical, Minneapolis, MN, USA; appendix). Pharmacokinetic studies show jejunal infusion of levodopa-carbidopa intestinal gel provides fairly constant plasma levodopa levels with less variability than oral formulations,[14,15] and open-label studies suggest a notable reduction (improvement) in off-time without worsening of dyskinesias.[16–19] Despite the absence of double-blind trials, levodopa-carbidopa intestinal gel is approved for use in 43 countries. However, open-label interventional studies in patients with advanced Parkinson's disease have frequently not been confirmed in double-blind trials.[20] Thus, we aimed to assess safety and efficacy of continuous levodopa-carbidopa intestinal gel infusion in patients with advanced Parkinson's disease in a prospective, double-blind, placebo-controlled setting.

See Online for appendix

Methods

Study design and participants

We undertook a 12-week, prospective, multicentre, placebo-controlled, parallel group, double-blind, double-dummy, double-titration study. We enrolled adults (aged ≥30 years) with advanced Parkinson's disease consistent with UK Brain Bank criteria that was complicated by off-periods which could not be satisfactorily controlled with optimised medical therapy. Optimised therapy was defined as an adequate trial in the judgment of the investigator of levodopa-carbidopa, a dopamine agonist, and at least one other class of anti-parkinsonian therapy (COMT inhibitor or MAO-B inhibitor). Participants must have received stable doses of levodopa for at least 4 weeks before enrolment in the study and had recognisable on-time and off-time with a minimum of 3 h of off-time per day based on a home diary assessment.[21]

Participants receiving sustained-release levodopa-carbidopa, Stalevo (Orion Pharma, Finland), or other formulations of levodopa were permitted into the study; doses were converted to equivalent doses of immediate-release oral levodopa-carbidopa and patients must have been on stable doses for at least 4 weeks before entry. Concurrent antiparkinsonian drugs (apart from apomorphine) were permitted if patients were on stable doses for 4 weeks before randomisation, and the dose was not changed during the study. Exclusion criteria included atypical or secondary parkinsonism, previous neurosurgical treatment for Parkinson's disease, clinically significant medical, psychiatric, or laboratory abnormalities in the judgment of the investigator, or any condition that might interfere with absorption, distribution, metabolism, or excretion of study drug or contradict placement of an intrajejunal percutaneous gastrojejunostomy tube.

After confirmation of eligibility by an independent enrolment steering committee, participants signed an informed consent form that was approved by the institutional review board at each participating site. We originally planned and started two identical studies to meet regulatory approval. However, after discussion with the regulatory authorities, who indicated that only one robust study was needed, the protocols and statistical analysis plan were amended to combine the studies while they were ongoing, before database lock and analysis of any data.

Randomisation and masking

Eligible participants were admitted to hospital for jejunal placement of a percutaneous gastrojejunostomy tube