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## Jejunal levodopa infusion in Parkinson's disease



Long-term oral levodopa therapy induces distressing on-off motor fluctuations in many patients with Parkinson's disease, probably because peripheral pharmacokinetic factors cause inadequate levodopa delivery to the striatum, generating central maladaptive changes.<sup>1</sup> Peripheral in this sense implies that levodopa is delivered to the brain in a discontinuous manner because of swings in plasma concentrations. Such oscillations result from levodopa's short plasma-elimination half-life and discontinuous duodenal absorption secondary to intermittent oral intake and erratic gastric emptying. Because of these issues, several adjustments to oral levodopa therapy have been proposed to reduce fluctuations, including a decrease in dose intervals, sustained-release formulations, and combination with dopa-decarboxylase or catechol-O-methyl transferase inhibitors.<sup>2</sup> Although partly efficacious, such strategies cannot control severe off-time states, and plasma concentrations fluctuate despite 40 years of efforts to improve levodopa pills. Therefore, constant infusion of soluble levodopa is an interesting alternative, although the physical and chemical properties of levodopa are not ideal for this strategy because it is poorly soluble and auto-oxidises quickly.

Several years ago, experimental intravenous levodopa infusions were tested for a few days in patients with Parkinson's disease; these infusions induced stable levodopa plasma concentrations and substantial improvements in off-time state.<sup>3,4</sup> However, volume of dilution, venous toxicity, and limitations in pump technology prevented use of this route for long-term treatment. Infusion of levodopa within the duodenum was then considered to bypass problems with gastric emptying. Initial positive results with a nasoduodenal tube<sup>5</sup> encouraged the development of Duodopa (AbbVie, North Chicago, IL, USA), a stable solution of levodopa-carbidopa, which is administered within the jejunum through a surgically inserted transabdominal port connected to an external pump.<sup>6</sup> Duodopa is approved in Europe for the management of patients with advanced Parkinson's disease and severe, disabling motor fluctuations that are not adequately controlled by oral therapy.

The evidence supporting this indication was restricted to small uncontrolled open-label trials, with

no double-blind randomised controlled study.<sup>7</sup> The placebo effect is strong in Parkinson's disease, especially for invasive procedures.<sup>8</sup> In this context, the trial reported in *The Lancet Neurology* by Warren Olanow and colleagues comparing levodopa-carbidopa intestinal gel to placebo fills a void, confirming infusion efficacy in a more rigorous manner. Compared with patients given immediate-release oral carbidopa-levodopa, patients who received levodopa-carbidopa intestinal gel had reduced off-time by 1.91 h (95% CI -3.05 to -0.76,  $p=0.0015$ ) and had improved activities of daily living and quality-of-life scores.<sup>9</sup> The overall reduction in off-state of more than 4 h associated with intestinal gel infusion was better than has been noted with oral antiparkinsonian drugs.

Comparison of different formulations of levodopa is challenging, and requires complex switch processes and dose adjustments. The investigators provided notable attention to ensure equivalent levodopa doses were given and masking was preserved by their use of a double-dummy, double-titration design. However, unmasking factors because of efficacy (as with any strongly efficacious intervention) or black colouration of the tube caused by levodopa oxidation might have enhanced placebo response on the active infusion. Unfortunately no formal assessment of masking was done. Patients on sustained-release levodopa-carbidopa formulations or Stalevo (Orion Pharma, Finland) had to be converted to immediate-release levodopa-carbidopa to allow double-blind adjustments during the trial. This design deprived the trial participants of the benefit of these drugs, thus favouring the active infusion. Moreover, forbidding changes in oral dosing frequency during the titration phase might have induced similar consequences, although notably off-time in the immediate-release oral levodopa-carbidopa group improved by 2 h compared with baseline during the trial, which is not insubstantial. Nevertheless, efficacy of levodopa infusion seems large enough not to be just an artefact, even if some artificial inflation cannot be excluded.

Despite the accomplishments of the intestinal gel infusion, it did not completely solve the patients' problems because 2 h off-time remained. Why? Central maladaptive changes might have persisted or require more than 3 months to regress. Alternatively, pharmacokinetic parameters might have improved

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insufficiently or do not depend on gastric emptying alone. Boluses of infusion, as done in routine practice were not permitted in the trial, which might have reduced efficacy. The effects of infusion on troublesome symptoms including non-motor fluctuations, falls, and dementia were not assessed, patients with dementia and falls were probably excluded, although this is not specified. The trial was small (71 patients) and short (3 months). This design prevents long-term conclusions and provided insufficient power to assess rare adverse events such as polyneuropathy and Guillain-Barré syndrome, or even more common ones such as impulse-control disorders. Notably, the effect of infusion on dyskinesias is unclear. No short-term worsening was observed, which is reassuring, and suggests that equivalent doses of levodopa were actually compared between both groups. However, the continuous dopamine stimulation hypothesis would predict improvement in dyskinesia on infusion.<sup>10</sup> This effect might not have been observed because patients did not have sufficient dyskinesia at baseline and were not followed-up for long enough to allow changes in cerebral plasticity. Nevertheless, the study cannot allow any firm conclusion about continuous dopamine stimulation.

Practically, levodopa jejunal infusion is not an easy solution to resolve off-time complications. It is a second-line therapy that is restricted to patients with severe off-time episodes, who are resistant to oral therapies. It is complex to implement. More than a third of the participating centres could not recruit more than one patient into the trial,<sup>9</sup> highlighting such difficulties. Most patients in the trial had adverse events related to surgery or the device, although these events were rarely serious. However, such complications are not uncommon after 3 months in everyday practice. Although no deaths were reported, these events can happen even in expert hands.<sup>11</sup> Indeed infusion therapy does not correspond to everyday practice for general neurologists and should be managed by specialised multidisciplinary movement disorders teams, who are familiar with patient's selection and device technology.

Finally, head-to-head comparisons have not

been done to assess the respective advantages and disadvantages of levodopa jejunal infusion versus the two main alternatives for management of severe problems with refractory off-time complications: continuous subcutaneous apomorphine infusion and functional surgery.<sup>3</sup> All these options are very expensive. For example, provision of Duodopa for 1 day costs about €100, which cannot be ignored and deserves careful assessment in terms of cost-effectiveness.

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