Two Decades of Evolving Care with Pump Therapies – What have we Learned?

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Abstract

Since the discovery that the gold standard treatment in Parkinson's disease (PD), oral levodopa, contributes to motor fluctuations, the treatment strategy of delivering dopaminergic drugs in a continuous manner has been investigated. Motor fluctuations are believed to be the result of a combination of progressive denervation of the striatum with advancing disease and erratic gastric emptying with oral levodopa, which leads to peaks and troughs in plasma levodopa concentration and thus pulsatile stimulation of dopaminergic neurons. Methods have been developed to provide continuous dopaminergic stimulation, such as the delivery of apomorphine by subcutaneous infusion and levodopa/carbidopa by intestinal gel infusion. These therapies have been shown to significantly reduce 'off' time and improve motor fluctuations, and therefore have been a major advance in the management of PD.

Keywords

Parkinson's disease, levodopa, continuous dopaminergic stimulation, subcutaneous apomorphine infusion, levodopa/carbidopa intestinal gel infusion

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Lessons Learned about Levodopa

Motor fluctuations in Parkinson's disease (PD) were described as early as 1969 by Cotzias et al.[1] Subsequent studies showed that many motor fluctuations were associated with low plasma levodopa levels (troughs) that occurred between oral doses of levodopa.[2] This phenomenon was called the end-of-dose deterioration or 'wearing-off' effect. In the 1970s and 1980s, clinical pharmacology research provided a great deal of information about oral levodopa and its relationship to the 'wearing-off' effect.

Levodopa benefits the patient from the very first dose but requires a few weeks to reach optimum effect. The stronger the initial response to the drug, the more prominent the subsequent motor fluctuations.[3] Increasing the dose of levodopa has been shown to prolong the duration of benefit, but does not increase the amplitude of response, and generally, the motor response wears off when plasma levodopa level drops to 50 % of the peak level, irrespective of the duration of benefit.[4]

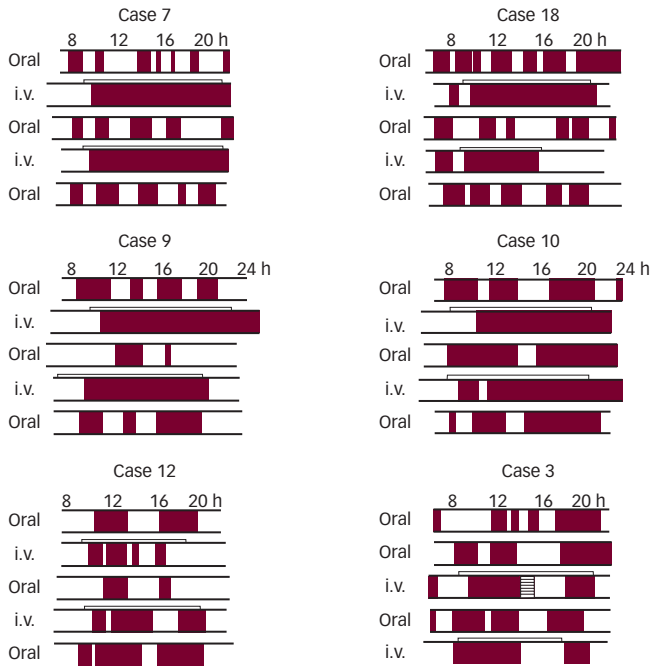
The 'On-off' Phenomenon

The most common manifestation of the 'on-off' phenomenon is inter-dose or peak-dose dyskinesia, which occurs at a rate of approximately 10 % per treatment year. As a result, after 10 years of oral levodopa treatment, almost all patients who are on significant doses of levodopa will have developed some dyskinesias.[5] Another form of dyskinesia is biphasic dyskinesias, which are much less frequent, partly because modern pharmacotherapies help to reduce their severity. These are particularly troublesome in young-onset patients, are extremely disabling and much more difficult to treat than peak-dose dyskinesias. 'Off'-period dystonia is another form that is often forgotten. Therefore, dyskinesias are not just one simple pattern of peak-dose dyskinesias.

In the 1980s, it was not clear whether 'off' periods were treatable. One theory was that during 'off' periods, patients were unresponsive to dopaminergic drugs, even at a high dose. However, this view began to be challenged by studies using continuous delivery of dopaminergic drugs.

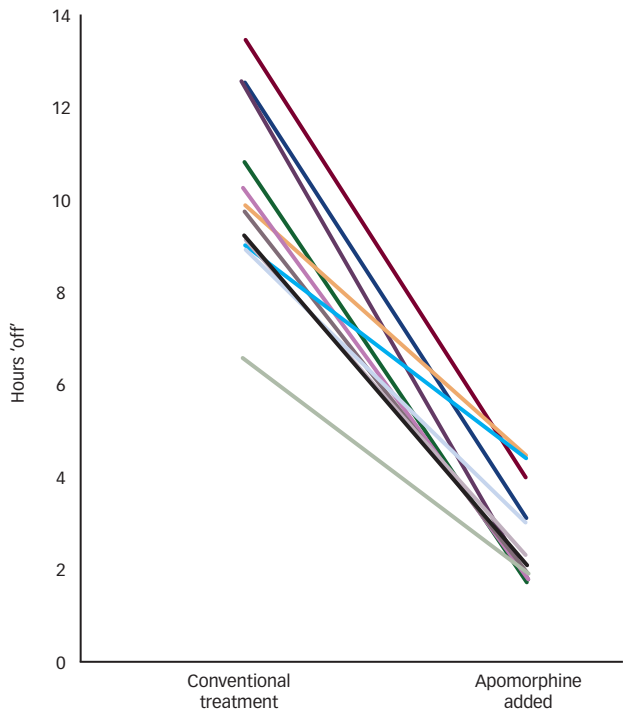
For example, in one study,[6] levodopa/carbidopa was administered to 14 patients with severe fluctuations. After three days, the patients received 200 mg of 5 mg/ml levodopa added to 250 mg saline (0.69 mg/ml) subclavian infusion. The dose was increased at two-hourly intervals until satisfactory control was achieved. On Days 4–7, there was a double-blind cross-over, and the patients received the intravenous levodopa infusion or placebo at a dose of 0.69 mg/ml

Figure 1: Diaries of Parkinson's Disease Patients with Severe Motor Fluctuations Receiving Levodopa Intravenously or Orally



Red-brown indicates 'on' time and white indicates 'off' time. i.v. = intravenous. Source: Adapted from RJ Hardie, AJ Lees, GM Stern, On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study, Brain*, 1984, 107, Pt 2, 487–506,[6] by permission of Oxford University Press.*

Figure 2: Effect of Apomorphine Infusion on Mean 'Off' Time per Day Averaged over a Week



Source: Adapted from The Lancet*, 331, CMH Stibe, PA Kempster, AJ Lees, GM Stern, Subcutaneous apomorphine in parkinsonian on-off oscillations, 403–6,[8] Copyright 1988, with permission from Elsevier.*

throughout the 12–16 hour infusion. The results showed that levodopa given intravenously at a constant rate brought about a marked and dramatic extension in the duration of mobility of these fluctuating patients and reduced the frequency of 'off' periods, compared with equivalent oral therapy (see *Figure 1*). Hardie and colleagues concluded that the development of a sustained-release formulation of levodopa would lead to improved control of response fluctuations.

Development of Apomorphine Infusion

At the same time as their studies on intravenous levodopa, Hardie et al.[6] explored the possibility of reversing patients' 'off' periods with parenterally active dopamine agonists. They performed a randomised double-blind study in which patients received lisuride, apomorphine (APO) or saline during their 'off' period. APO consistently reversed 'off' phases when given shortly after their onset, while lisuride was less effective. These results confirmed that 'off' periods were amenable to dopaminergic therapy. This suggested that a consistent delivery of exogenous dopamine to dopaminergic receptors may alleviate motor fluctuations.

There were two advances in other medical therapies in the mid-1980s that had an important impact on the development of antiparkinsonian treatments able to provide more continuous dopaminergic stimulation (CDS). One was the marketing of domperidone as an antiemetic that did not cross the blood-brain barrier and did not block the striatal dopamine receptors, as opposed to the other neuroleptics that were the standard antiemetics. This drug enabled further advancement of studies with APO, which is a powerful emetic.

The other advance was developments in the insulin pumps used for diabetes treatment. These in turn helped in the development of pumps to infuse lisuride[7] and then APO.[8] In patients who were levodopa-responsive but had very severe refractory fluctuations, APO infusion led to a decrease of 6.3 hours in the mean duration of daily 'off' periods over a period of 15 months (see *Figure 2*).[8] APO infusion also had good results in patients with refractory 'on-off' fluctuations that were not controlled by oral medication or subcutaneous intermittent rescue injections. Adverse effects observed with APO infusion included eosinophilic panniculitism,[9] which was the most frequent adverse event. Christmas and colleagues also showed that autonomic 'off'-period phenomena could be reversed by CDS. Subcutaneous administration of APO in PD patients with urinary symptoms led to improvements in voiding efficiency, with increased mean and maximum flow rates and a reduction in post-micturition residual volume.[10]

Development of Levodopa/Carbidopa Intestinal Gel Infusion

Oral levodopa/carbidopa was developed in the late 1980s, but efforts continued to produce a formulation that could provide more CDS and be both commercially and practically feasible. Levodopa solubility is poor and therefore, technical improvements were needed to produce a solution of low enough volume to be deliverable in a portable pump.[11] In the 1990s, Kurth et al.[12] achieved steady plasma levodopa levels with a levodopa/carbidopa/ascorbic acid solution, which led to a marked reduction in 'off' periods in patients. The solution was delivered duodenally, which overcame the problem of erratic gastric emptying with oral levodopa that leads to peaks and troughs in plasma levodopa concentration and thus pulsatile stimulation.

Sage et al.[13] titrated duodenal levodopa infusions at a rate aimed at maintaining the patient in a just 'on' state over time. Their small study demonstrated that progressively less levodopa was needed to keep the patients in the 'on' phase in the first 60 days, after which the dose

remained stable. In patients with severe diphasic dyskinesias treated by continuous levodopa infusion, if the infusion rate was increased, the diphasic dyskinesias were alleviated for a period of time and then returned.[14] Therefore, there continued to be a breakthrough of control.

A long-term study[11] confirmed that enteral levodopa infusion was an effective treatment for motor fluctuations, but the poor solubility of levodopa in aqueous solution (2 mg/ml) led to the use of cumbersome pumps that were not very practical. Nyholm et al.[15] later discovered that the addition of carboxymethyl cellulose gel to levodopa/carbidopa solutions provided a more stable compound. The gel enables levodopa concentrations of up to 20 mg/ml to be delivered and means that a cassette containing only 100 ml levodopa/carbidopa intestinal gel (LCIG) is a sufficient daily dose for most patients. LCIG infusion has been shown to significantly reduce pre-existing levodopa-induced dyskinesias.[11,16,17]

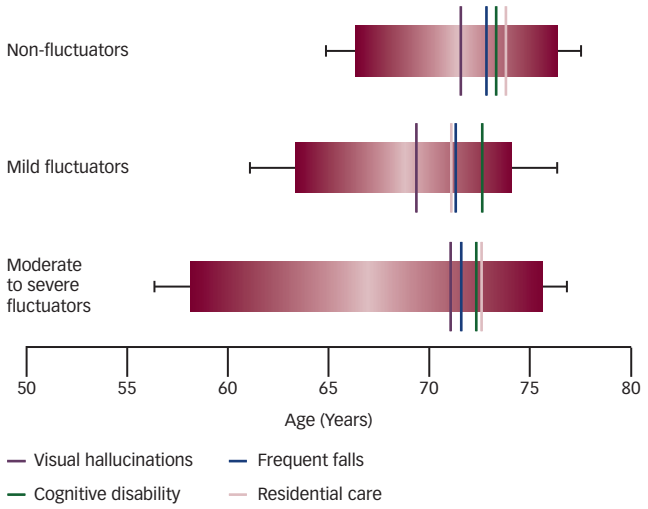
Patterns of Levodopa Response in Parkinson's Disease

Studies that shed light on patterns of levodopa response/disease progression can contribute to a better understanding and prediction of the disease progression. In turn, this may enable more optimal CDS treatment selection and timing of treatment.

In a clinico-pathological study, the pathological findings for patients who had developed disabling levodopa-induced motor fluctuations and a stronger therapeutic response ('fluctuators') were compared with patients who had a more modest but stable levodopa response ('non-fluctuators').[3] Kempster et al. found that fluctuators had a younger age of onset and a longer disease course, but the mean age at death was almost the same as in non-fluctuators. There was no difference either in the distribution of Lewy body burden or other pathologies. In addition, four milestones of advanced disease (frequent falls, visual hallucinations, cognitive disability and need for residential care) occurred at a similar time from death in each group (see *Figure 3*). The interval from the first milestone to death was not proportional to the duration of disease. The fluctuators and non-fluctuators reached a common pathological endpoint at a similar age, with a similar duration and manifestations of end-stage disease. The results showed that the late clinical and pathological progression of PD may have a non-linear or exponential relationship with time.

Last year, a follow-up paper was published in which the relationships between age, the advanced clinical stages of PD and neuropathology were investigated.[18] It was demonstrated that the advanced stage of PD progressed in a similar way with a common pathological endpoint regardless of the age of onset. The clinico-pathological comparisons for the final stage of the disease support a staging system based on the rostral extent and severity of Lewy body pathology, although other pathologies may have a synergistic role in causing cognitive disability. These observations about age and advance of the disease are best explained by an exponential curve for clinical progression. The chief effects of age on the rate of disease progression were observed over the early-middle phase of the disease process. Hence, this suggests that the early-middle phase is the optimal period when CDS can be used.

Figure 3: Milestones of Parkinson's Disease Advancement and Total Disease Course



Error bars indicate standard error of the mean. The red rectangles represent disease duration. Source: PA Kempster, DR Williams, M Selikhova, J Holton, T Revesz, AJ Lees, Patterns of levodopa response in Parkinson's disease: a clinico-pathological study, Brain*, 2007, 130, 8, 2123–8,*[3] *by permission of Oxford University Press.*

Conclusions

Motor fluctuations develop with time in patients on oral levodopa. These fluctuations are believed to be the result of a combination of progressive denervation of the striatum with advancing disease and erratic gastric emptying with oral levodopa, which leads to peaks and troughs in plasma levodopa concentration and thus pulsatile stimulation of dopaminergic neurons. The development of methods to continuously deliver dopaminergic drugs, such as subcutaneous APO infusion and LCIG infusion, has reduced motor fluctuations in patients. New data suggest that the early-middle phase of PD is a window of time in which CDS therapies can be used optimally. A point of discussion is whether CDS treatment should be initiated earlier than it is currently. ■

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