Management of Parkinson’s Disease

a report by
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Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease, and is responsible for significant morbidity and costs. Current treatments target the replacement of dopamine loss through the administration of dopaminergic agents such as levodopa (converted to dopamine in the brain) and dopamine agonists. Several medications have been tested for neuroprotection, but results so far are inconclusive. Symptomatic therapies allow good motor control for many years, until cognitive impairment and balance problems develop.

Risk–Benefit Assessment of Current Dopaminergic Medications

Levodopa is the gold standard for treatment of Parkinson’s disease, but its oral administration is associated with a high risk of motor fluctuations and dyskinesia. This is due primarily to the pulsatility of oral administration in combination with the progressive loss of dopamine nerve terminals.

Dopamine agonists have been widely used in recent years because their long-term utilisation reduces the risk of motor fluctuations and dyskinesia. They are divided into two classes:

- ergot (pergolide, cabergoline); and
- non-ergot (pramipexole, ropinirole and rotigotine).

The use of ergot dopamine agonists has recently decreased significantly as their intake is associated with pleuro-pulmonary or reperitoneal fibrotic reactions, as well as heart valvulopathy. The latter in particular is viewed with concern because severe regurgitation may require heart valve replacement, which increases the disability of patients. The mechanism of heart valvulopathy is mediated by the 5-HT_{2b} agonistic activity of pergolide and cabergoline on serotonergic receptors expressed on cardiac valvular fibroblasts.

In addition to performing a population study, we recently reviewed the available literature and found that the frequency of moderate to severe regurgitation in patients receiving cabergoline and pergolide is markedly increased compared with patients treated with non-ergot agonists and non-Parkinson controls (see Table 1 and Figure 1). This evidence led to the withdrawal of pergolide marketing authorisation in the US, while in Europe the prescription of both pergolide and cabergoline is restricted.

Another issue concerns the risk of psychiatric adverse events such as addictive behaviour, pathological gambling and hypersexuality. We recently assessed the frequency of these disturbances using specific scales in a cohort of PD patients and non-PD controls. Overall, 28% of the PD patients and 20% of the healthy controls reported at least one abnormal behaviour. PD patients had higher scores than controls for impulsivity, compulsivity and depression; however, there was no correlation between impulsivity, compulsivity and depression scores in PD. Male gender and higher impulsivity score, but not dose and kind of dopaminergic medications, were associated with increased probability of impulse control disorders in PD. We concluded that individual susceptibility factors such as impulsivity and depression underline abnormal behaviours in PD patients treated with stable dopaminergic therapy.

Management of Advanced Disease

Strategies to control motor complications include increasing the frequency of levodopa administration, co-administering levodopa with the catechol-O-methyltransferase (COMT) inhibitors entacapone or tolcapone and/or use of the monoamine oxidase type B (MAO-B) inhibitor rasagiline. The benefit thus obtained allows adequate motor control for many years, but eventually patient motor conditions deteriorate, requiring more invasive interventions. Deep brain stimulation of the subthalamic nucleus (STN-DBS) is widely available, but cannot be performed in patients over 70 years of age or in those presenting with cognitive or psychiatric disturbances.

Ideally, one would infuse levodopa at constant rate, but this approach has been hampered by its poor solubility in water, which makes intravenous infusion impractical. The breakthrough came from the creation of a stable concentrated levodopa–carbidopa gel (Duodopa®, Solvay), 100ml of which is equivalent to 3,000ml of water containing levodopa. This 100ml cassette contains 2,000mg of levodopa and 500mg of carbidopa, enough for around 16 hours of infusion.
The intra-intestinal infusion of levodopa–carbidopa is typically divided into two phases. The first is a test period using a temporary nasal tube; this phase is not always necessary if a patient’s response to levodopa is well known. There is, of course, no such test period available for DBS, while apomorphine may be used as a shot injection. The use of a test period helps to familiarise the patient with the effect of continuous dopaminergic stimulation with Duodopa; while in our experience transition to permanent Duodopa has occurred in 100% of patients, other centres have had people decide not to continue. The procedure to implant the catheter into the duodenum is via percutaneous endoscopic gastrostomy (PEG). Given that the tip of the catheter is in the duodenum and absorption of the compound is almost immediate, benefit can be seen very quickly from the administration of Duodopa.

Our experience with this procedure consists of the prospective evaluation of 22 PD patients (13 male, nine female) with Hoehn and Yahr staging (H&Y) ≥3 who fulfilled UK brain bank diagnostic criteria. Patients were recruited from different institutions, including the Parkinson Institute in Milan (n=14) and the Parkinson and Movement Disorders Centres of the Universities of Pavia and Turin. All patients presented with motor fluctuations and dyskinesias that could not be controlled with levodopa and dopamine agonist oral treatment. None of them had dementia according to Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria, and mini mental state examination (MMSE) score was >24. We did not consider patients with active hallucinations or those under treatment with neuroleptics for this procedure.6,7

We found a long-standing significant reduction in ‘off’ time in patients with advanced PD during continuous duodenal infusion of levodopa–carbidopa. More importantly, this was paralleled by a significant decrease of dyskinesias despite overall unchanged total levodopa doses. These results were obtained in a selected cohort of patients without cognitive abnormalities who fulfilled inclusion criteria similar to those for DBS, with the exception of age. Our evaluations were open-label but, given the magnitude of the clinical changes, we feel that the benefits cannot be attributed to a placebo effect. Motor benefit was associated with improved quality of life at advanced disease stage, reflected in all activities of daily living (see Figure 2).

Interestingly, we found that the improvement was mainly in dyskinesia severity; overall duration did not change. However, mild dyskinesias are generally not associated with significant disability in PD. The reduction of the duration of the off period was expected, as continuous infusion allows stable levodopa plasma levels throughout the day. The mechanism of ‘wearing off’ and dyskinesia development is still uncertain, although both disease progression and the pulsatility of oral levodopa are likely to contribute. Indeed, early treatment with dopamine agonists may reduce the risk of motor complications because they ensure relatively stable stimulation thanks to their long half-life. Our study confirms the effectiveness of levodopa–carbidopa infusion and, importantly, shows that a therapeutic window exists and can be maintained long-term even in advanced and complicated cases.

Our findings also expand on previous studies that reported the potential benefits of levodopa duodenal infusion in both prospective and retrospective evaluations. Although pharmacokinetic data were not collected, our results are consistent with a previous report on levodopa duodenal infusion, demonstrating reduced fluctuations in plasma levodopa concentrations during continuous infusion compared with oral therapy. Since we did not find differences in total dopaminergic medication doses compared with baseline, we believe our findings provide further evidence that the pulsatility of oral administration rather than levodopa itself is responsible for the development of motor complications.

Other studies have shown that the continuous infusion of dopamine agonists (lisuride or apomorphine) may improve motor conditions in patients with advanced PD, particularly by reducing wearing-off, but benefits on dyskinesia are uncertain. We recently reported that apomorphine infusion markedly reduced the duration of the off period, but did not modify dyskinesia severity or duration. In contrast,

### Table 1: Overall Results from Published Studies

<table>
<thead>
<tr>
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<th>Abnormal/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pergolide</td>
<td>55/245</td>
<td>22%</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>35/102</td>
<td>34%</td>
</tr>
<tr>
<td>Non-ergot</td>
<td>81/181</td>
<td>44%</td>
</tr>
<tr>
<td>Non-PD controls</td>
<td>11/177</td>
<td>6%</td>
</tr>
</tbody>
</table>

PD = Parkinson’s disease.

### Figure 2: Quality of Life Improvement During Duodopa Duodenal Infusion
Parkinson’s Disease

improvements obtained with duodenal levodopa infusion resemble, in our experience, those observed during STN-DBS in terms of motor and quality of life changes. It should be noted that STN-DBS produces a round-the-clock benefit while levodopa duodenal infusion is generally stopped at night-time, resulting in the reappearance of motor symptoms. Withdrawals (n=5) occurred during the first few months of treatment. Four of these were due to the development of confusion or hallucinations, while the fifth was due to unrelated peripheral polyneuropathy. Overall, we believe that this treatment should be applied primarily to patients with a good level of compliance, no cognitive impairment and, possibly, without previous history of psychiatric disturbances.

In summary, levodopa–carbidopa duodenal infusion improved motor conditions and reduced disabling dyskinesia in patients with advanced PD, resulting in significant benefits in quality-of-life measures. Our results suggest that this treatment strategy can widen therapeutic options in complicated PD patients. Conclusion

In conclusion, therapeutic options in advanced PD are limited and more complex strategies need to be considered in these patients. Apomorphine infusion is easy to perform and the pump that supplies the subcutaneous infusion is light and easy to use. However, the effectiveness of apomorphine has been demonstrated only in open-label studies and it does not appear to improve dyskinesia. In addition, patients usually continue to take oral levodopa. Both continuous duodenal levodopa administration and STN-DBS provide significant motor benefit, but DBS is more invasive and evidence is accumulating that the behavioural and cognitive changes associated with DBS may not be reversible. In contrast, duodenal levodopa administration in this group of patients produced no abnormal changes in behaviour or cognition. In addition, our follow-up results show that levodopa infusion can lead to significant clinical benefit and that a therapeutic window can be identified even in complicated PD patients. According to our experience, duodenal levodopa infusion should be considered in PD patients with advanced disease and motor complications that cannot be controlled with standard oral treatment.

Now they can.

Parkinson’s Disease don’t normally belong in the same sentence.

Now they can.

Improved quality-of-life and advanced Parkinson’s Disease don’t normally belong in the same sentence.

Now they can.

Duodopa® contains 1 ml contains 20 mg levodopa and 5 mg carbidopa monohydrate. 100 ml contain 2000 mg levodopa and 500 mg carbidopa monohydrate.100 ml contain 2000 mg levodopa and 500 mg carbidopa monohydrate.

Dosage:
The morning bolus dose is administered by the pump to rapidly achieve the therapeutic dose level (within 10-30 minutes). The total morning dose should not exceed 15 ml (300 mg levodopa). Continuous maintenance dose: The maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The continuous maintenance dose is adjusted individually. It should be kept within a range of 1-10 ml/hour (20-200 mg levodopa/hour). Extra bolus doses: To be given as required if the patient becomes hypokinetic during the day. The extra dose should be adjusted individually. Treatment must be monitored.

Contraindications:
Hypersensitivity to levodopa, carbidopa or any of the excipients; severe liver and renal insufficiency; severe heart failure; severe cardiac arrhythmia; acute stroke. Special warnings and precautions for use: Duodopa should be administered with caution to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions. In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments. All patients treated with Duodopa should be monitored carefully. Patients with past or current psychosis and chronic wide-angle glaucoma can be treated with caution.

Adverse effects:
Most prominent clinical symptoms of an overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasm can be an early sign of overdose. The treatment of an acute overdose of Duodopa is in general the same as that of an acute overdose of levodopa. Electrocardiographic monitoring should be used and the patient observed carefully for the development of cardiac arrhythmias; if necessary an appropriate antiarrhythmic therapy should be given. The possibility that the patient took other medicinal products together with Duodopa should be taken into consideration. To date experiences with dialysis have not been reported, therefore its value in the treatment of overdose is unknown. Special precautions for storage: store in a refrigerator (2ºC-8°C). Keep the cassette in the outer carton in order to protect from light. The marketing holder of the product is Solvay Pharmaceuticals. For further information consult www.solvaypharmaceuticals.com

References: