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Subcutaneous continuous apomorphine infusion in fluctuating patients with Parkinson's disease: long-term results

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Abstract Fluctuations in motor disability and dyskinesias are the major problem in the long-term treatment of Parkinson's disease (PD). Many authors and ourselves have shown that by giving patients a continuous infusion of levodopa it is possible to control motor fluctuations. Levodopa can be administered continuously only by intravenous, intragastric or intrajejunal delivery. Continuous dopaminergic stimulation can be achieved more easily by infusing dopamine agonists subcutaneously. Apomorphine is a potent water-soluble dopamine receptor agonist that has been shown to successfully control motor fluctuation when subcutaneously infused in complicated parkinsonian patients. We report the clinical data of 30 PD patients having at least five years of treatment with subcutaneous continuous apomorphine infusion.

Introduction

The management of Parkinson's disease (PD) patients with complicated motor fluctuations represents a major and not infrequent problem. These patients swing between periods of mobility, often accompanied by severe dyskinesias, and periods of drug-resistant akinesia [1]. Evidence suggests that many of these phenomena directly reflect oscillations in levodopa plasma levels and the rate of levodopa transport to the brain. Indeed the fluctuations in motor performance occur frequently when levodopa is administered intermittently, but much less often when it is administered continuously [2]. Unfortunately, levodopa is not suitable for chronic parenteral therapy in outpatients, as it requires high volumes of solution to be administered intravenously [3]. It is often difficult to ensure the presence of adequate plasma levels of levodopa throughout the day using standard oral formulation.

Apomorphine is a potent water-soluble dopamine receptor agonist that has been shown to successfully control motor fluctuation when subcutaneously infused in complicated parkinsonian patients [4-7]. We report the clinical data for 30 PD patients having at least five years of treatment with subcutaneous continuous apomorphine infusion. The crucial point is to evaluate efficacy and tolerability of this route of dopamine agonist administration after several years of treatment.

Patients and methods

We analysed the clinical data for 30 patients who received continuous subcutaneous apomorphine infusion for at least five years. The 30 fluctuating parkinsonian patients had been previously treated with oral levodopa preparation and other antiparkinsonian medication. We excluded for this treatment patients over 70 years of age, patients with previous history of psychiatric side effects from dopaminergic agents, those without a good response to levodopa, those suffering from dementia, heart disease problems, or other severe systemic disorder. At the begin of apomorphine infusion, the patients, 21 men and 9 women, had a mean age of 62.0 $\pm$ 8.5 years, a mean duration of disease of 14.8 $\pm$ 5.5 years, and a severity of disease of 4.2 $\pm$ 0.8 on Hoehn and Yahr stage. They were on pharmacological treatment for 14.6 $\pm$ 4.7 years, with a mean levodopa dosage of 708 $\pm$ 245 mg/day, tritrated in 4.1 $\pm$ 2.3 administrations during the day. Previous consensus was obtained, we started the treatment with apomorphine at the initial dosage of 2 mg/hour. All patients received oral domperidone (60 mg/day) pre-treatment to prevent systemic side effects. Apomorphine was administered by a modified insulin pump programable for varying infusion rates according to the patients' individual daytime requirements. These pumps can deliver between 0.1 and 5 ml of solution containing 1-50 mg apomorphine per hour. Catheters of different lengths can be used to ensure the patient's maximum comfort. The needle was placed subcutaneously into the abdominal wall, and was changed every day. The infusion rate was gradually increased according to therapeutic requirements of the patients. Subcutaneous apomorphine was administered without any additional antiparkinsonian medication between 8 a.m. and 8 p.m., and discontinued overnight. This regime was maintained for about one week, increasing the dose to obtain the best clinical response. In those patients not completely mobile or still fluctuating during apomorphine infusions, oral levodopa plus a peripheral decarboxylase inhibitor was added, starting with a single morning dose.

Results

Apomorphine dosage averaged 4.3 $\pm$ 2.9 mg/h during the 12-hour infusion in all 30 patients (range, 2.5-8.0), and did not change significantly with time. Figure 1 shows the average oral levodopa dosage in patients throughout the 5 years of apomorphine infusion. Compared with pre-infusion levodopa intake, daily oral levodopa dosage fell by about two-thirds during the period of infusion (pre-infusion mean levodopa dosage for all 30 patients was 708 $\pm$ 324 mg/day, falling to 375 $\pm$ 176 mg/day after leaving hospital once stabilized; $p<0.0001$). Oral levodopa dosage did not change significantly during the follow-up period on infusion.

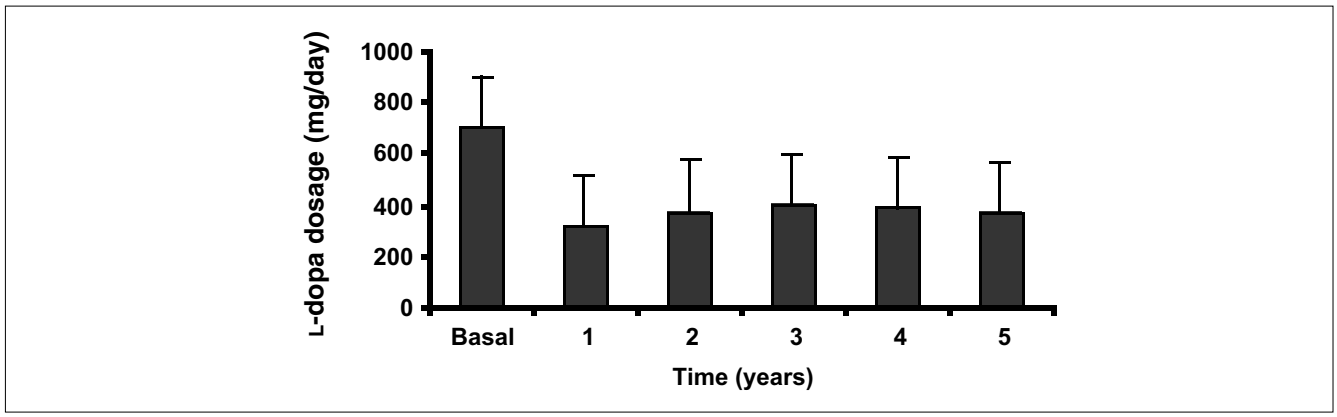

Fig. 1 Mean levodopa dosage administered over 5 years

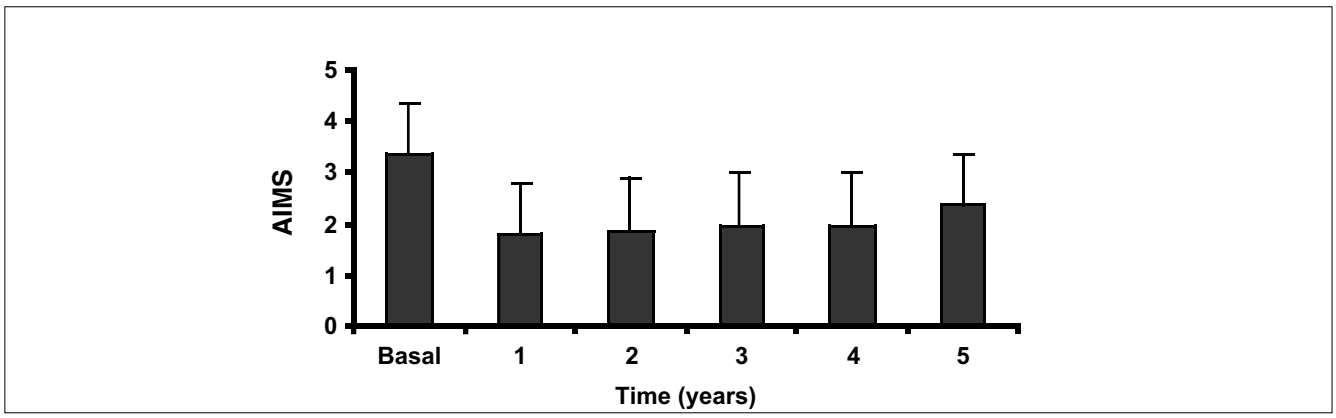

Fig. 2 Abnormal involuntary movements (AIMS) over 5 years of treatment

Abnormal involuntary movements were also reduced during the early time of lisuride infusion. Figure 2 shows that as apomorphine infusion were continued for up to 5 years there was a tendency for dyskinesias to return after some years, but never to the pre-infusion levels. The acute side effects were mainly nausea and dizziness, which disappeared after 7-10 days of treatment. During the chronic treatment phase almost all of the patients developed distressing skin reactions at the injection site.

Discussion

Apomorphine infusion reduced levodopa dosage, reduced time spent "off" and improved dyskinesias in complicated parkinsonian patients. The technique is demanding, but can be managed relatively easily, especially if patients must be hospitalised for the initial clinical evaluation and administration. We suggest that the continuous dopaminergic stimulation made with subcutaneous infusion of apomorphine can be successful in controlling motor fluctuations in selected parkinsonian patients.

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