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Translation of full original text

Therapeutic experience with a slow-release preparation of levodopa (‹Madopar› HBS) in patients with advanced Parkinson's disease

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Summary

15 patients with Parkinson's disease who had been experiencing fluctuations in response to conventional ‹Madopar› therapy were switched over to the slow-release preparation ‹Madopar› HBS. 12 patients showed a positive response, with a reduction in the daily number of 'off' phases and an increase in 'on' time (daily total number of hours with symptoms well under control). The daily amount of levodopa required under ‹Madopar› HBS therapy was some 65% higher on average than under the previous conventional ‹Madopar› therapy. Additional individual doses of standard ‹Madopar› were also necessary during treatment with the slow-release preparation. Biphasic dyskinesia and 'off-period' dystonia were less marked under ‹Madopar› HBS, while peak-dose dyskinesia increased in comparison with conventional ‹Madopar› therapy. During follow-up of 37 to 543 days (mean: 217 days) the effect of therapy with ‹Madopar› HBS proved stable in 9 of the 12 initial responders.*

*Trade Mark

More than half of all patients with Parkinson's disease develop fluctuations in response to levodopa after three to five years of substitution therapy[5, 16]. The term on-off effect was coined for these swings[1, 6], which comprise two basic types of fluctuation. Most of the patients affected experience fluctuations in their clinical state that are recognizably related to the dosing intervals and/or plasma levels of levodopa[17]. Thus the effect of the levodopa subsides at regular intervals (wearing-off effect), causing nocturnal or early-morning akinesia in particular. In 10–20% of the patients affected, the levodopa effect undergoes apparently random interruptions of an abrupt nature (on-off effect in the strict sense of the term).

The pathophysiology of these swings has not been satisfactorily elucidated[8]. The findings of positron emission tomography suggest a decline in striatal storage capacity for 18F-fluorodopa as the disease progresses and therefore as dependence on a steady exogenous supply of levodopa increases[13]. This theory would chime with the

repeatedly demonstrated fact that fluctuations in effect are largely offset by continuous i.v. infusion of levodopa[21,25].

In the last few years these findings have led to the development of two approaches to dealing with fluctuations in the efficacy of long-term levodopa therapy: continuous subcutaneous administration of dopaminergic agonists by means of minipumps[19], and oral administration of slow-release levodopa preparations (delayed gastrointestinal release of the active ingredient). Positive results were obtained with the latter approach in a hospital setting over an observation period of several weeks[20]. The present paper reports on the results obtained in long-term outpatient treatment with the slow-release preparation ‹Madopar› HBS in patients with Parkinson's disease experiencing fluctuations in effect.

Patients and methods

15 patients with advanced Parkinson's disease were treated with ‹Madopar› HBS. The main clinical data are presented in Table 1. All patients exhibited a long-term levodopa syndrome with fluctuations in effect and drug-induced dyskinesia. Swings of the wearing-off type and marked nocturnal or early-morning akinesia were experienced by all patients but no non-dose-dependent random fluctuations in symptoms were reported. Levodopa-induced motor restlessness was present in 8 patients in the form of choreatic peak-dose dyskinesia. 6 patients suffered from foot dystonia associated with off-phases (off-period dystonia), and 9 from biphasic, choreatic-dystonic dyskinesia.

Table 1
Clinical data ($n = 15$; 10 males, 5 females)

‹Madopar› HBS	
Age	61 (45–76) years
Time since onset of disease	11.4 (7–16) years
Hoehn + Yahr stage	
On	2.1 (1–4)
Off	3.5 (2–5)
Levodopa therapy	
– duration	9.4 (4–16) years
– daily dosage	1,050 (400–2,200) mg
Additional medication	
– bromocryptine	3 patients
– procyclidine	2 patients
– biperiden	1 patient
– trihexyphenidyl	1 patient
– lisuride	1 patient

The switchover from the previous standard ‹Madopar› treatment to the slow-release form was undertaken in hospital. At the same time, patients were shown how to keep a personal 'mobility calendar' in which they had to enter hourly self-ratings of mobility (scale: good/moderately good/poor) (Figure 1). The daily dosage and number of doses of the previous levodopa treatment was adapted as required, until optimal clinical results were obtained. All other antiparkinsonian medication was continued unchanged.

After being observed in hospital for at least one week under 'optimal' individualized therapy with conventional ‹Madopar›, the patients were switched over to the

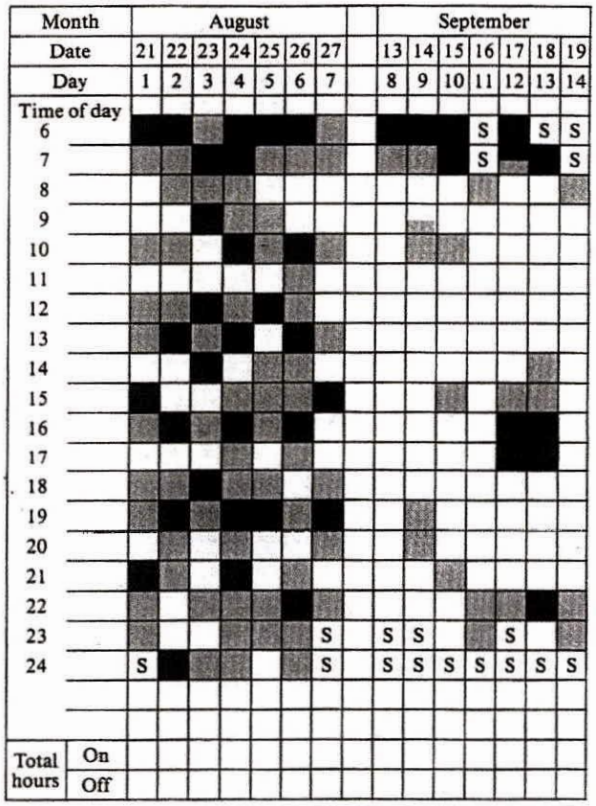

Figure 1. On/off calendar for hourly rating of mobility by patient W. H. for one week under optimum standard ‹Madopar› (21–28 August) and ‹Madopar› HBS (13–19 September) therapy. Poor (off) ■; good (on) □; intermediate stage ▒; sleep [S].

slow-release preparation (‹Madopar› HBS), though the daily amount of levodopa administered remained initially unchanged. On the basis of earlier experience[20], the first morning dose consisted of equal amounts of the conventional and the slow-release form of levodopa. Then the daily dosage and the number of daily doses, including any back-up doses of conventional ‹Madopar›, were adjusted until the optimal clinical effect was achieved, at which point the patients were discharged. The hospital stay lasted three weeks on average. Clinical evaluation during outpatient follow-up was based on the mobility calendar kept by the patient (for one week prior to each outpatient appointment), the Columbia University Rating Scale (CURS), the Northwestern University Disability Scale (NUDS), and the Hoehn and Yahr staging. Levodopa-induced dyskinesia was rated on a 0–4 scale; for biphasic dyskinesia and off-period dystonia the average number of episodes a day was additionally determined by questioning. The average number of 'good' (on) and 'poor' (off) hours per day, and the severity of nocturnal and early-morning akinesia (0–4 scale) were also determined by questioning, with the aid of the mobility calendar which was presented at each appointment. The outpatient check-ups were held every two months.

Results

During the switchover to ‹Madopar› HBS in hospital, 12 of the 15 patients exhibited a positive response and were accepted for outpatient follow-up. In 3 patients (early treatment failures), unacceptably long periods of immobility (off phases) and the subjective unpredictability of the time to effect of an individual dose for the patient led to withdrawal of the slow-release preparation during the hospital stay.

Table 2 presents an overview of the key parameters of therapy with the conventional and the slow-release forms in the 12 evaluable patients. Mean follow-up was 217 (37–543) days for treatment with ‹Madopar› HBS. As can be seen from the table, the optimum therapeutic daily dosage of levodopa was 65% higher than in the previous conventional treatment. This increased daily dosage included additional back-up doses (an average of 160 mg daily administered in up to three doses) of conventional ‹Madopar›. The number of daily doses and the dosing interval were only very slightly changed by the switchover to slow-release ‹Madopar› HBS (Table 2).

All 12 evaluable patients exhibited a reduction, in some cases considerable, in the daily number of off periods during treatment with ‹Madopar› HBS, together with a clear increase in the on time (total number of hours with symptoms well under control) (Table 3).

Table 2
Optimum treatment schedules ($n = 12$)

‹Madopar›		‹Madopar› HBS
	Mean daily dosage levodopa total	
700 mg (350–1,200 mg)		1,160 mg (500–2,100 mg)
	of which HBS	1,000 mg (400–1,800 mg)
	back-up	160 mg (100–300 mg)
	Mean number of doses	
6 daily (4–8 daily)		5.2 daily (3–6 daily)
	Mean dosing interval	
3 hours (2–4 hours)		3.2 hours (2.5–5 hours)
	Mean duration of therapy	217 days (37–543 days)

Table 3
Results: fluctuations ($n = 12$)

‹Madopar›		‹Madopar› HBS
	Mean number of off phases daily	
8 patients	>3	–
4 patients	1–3	10 patients
–	0	2 patients
	Mean 'on' hours daily	
7.1 (4–11)		9.8 (9–14)

Figure 1 illustrates a patient's mobility calendar before and after the switchover to slow-release ‹Madopar› HBS. A comparable reduction occurred in nocturnal akinesia (mean score down from 2.3 to 1.2) and early-morning akinesia (score down from 2.2 to 1.6), while the mean duration of uninterrupted sleep increased.

Levodopa-induced motor restlessness had been present in all patients under conventional therapy, with 8 of the 12 evaluable patients exhibiting largely biphasic, and 7 monophasic, peak-dose dyskinesia. 4 patients experienced painful off-period foot dystonia. While off-period dystonia and biphasic dyskinesia declined in intensity and frequency after the switchover to ‹Madopar› HBS, an overall increase occurred in peak-dose dyskinesia, which was eventually reported in all 12 patients, in pronounced form in 4 of them (Table 4).

Table 4
Results: dyskinesia ($n = 12$)

‹Madopar›		‹Madopar› HBS
	Peak-dose severity	
–	4	2
1	3	2
3	2	3
3	1	4
	Biphasic frequency	
6	>3	0
2	1–3	7
	off-period severity	
1	4	–
2	3	–
1	2	2
–	1	–

An adequate antiakinetic effect was not achieved with ‹Madopar› HBS in 3 of the 15 patients, and the treatment had to be withdrawn after 5, 6 and 18 days, respectively, on account of prolonged off periods (see above). A further 3 of the 12 initial responders to slow-release therapy were switched back to conventional ‹Madopar› during outpatient follow-up ('late' treatment failures). This became necessary in 1 patient after 37 days of treatment on account of daily semi-on states lasting several hours, during which the patient's mobility remained poised to a subjectively unacceptable extent between his accustomed good (on) and bad (off) phases. 2 other patients experienced episodes of severe choreoathetotic dyskinesia after ‹Madopar› HBS treatment of three and seven months, respectively; these episodes sometimes lasted for hours, particularly in the afternoon, and therefore nullified the functional benefits of levodopa.

Discussion

A number of clinical investigations have demonstrated that slow-release forms of levodopa have a beneficial effect on dose-dependent fluctuations in efficacy[2, 3, 11, 12, 20, 23, 24]. The observation periods in most of these studies were relatively short (less than six months) and therefore the value of such treatment in the long term was not clear. In addition, several authors reported initially disappointing results with ‹Madopar› HBS in patients with advanced Parkinson's syndrome and swings in response[9, 10, 22].

The observation period in the present investigation lasted up to 1.5 years. A sustained positive response to ‹Madopar› HBS was demonstrated in 9 of 15 patients, with minimizing of fluctuations in effect, increase in the daily on phases (good control of symptoms), and decrease in nocturnal and early-morning akinesia. The daily dosages of levodopa required were an average of 65% up on those of conventional ‹Madopar›. This means that the bioavailability of ‹Madopar› HBS was about 60% less than that of standard ‹Madopar›[4, 15]. Some of the poor therapeutic results reported in a number of publications were due to switching over from conventional ‹Madopar› to ‹Madopar› HBS at a 1:1 dosage ratio[10, 14].

Contrary to theoretical expectations and in line with earlier studies[20, 22], treatment with the slow-release form in this group of patients did not result in any appreciable lengthening of the dosing interval. A major element of treatment failure in earlier investigations with ‹Madopar› HBS, compared with standard ‹Madopar›, was the longer time to onset of action after ingestion, together with the patients' subjective impression of poor predictability of effect[9, 22]. This delay can be explained by the single-dose pharmacokinetics of ‹Madopar› HBS, with the peak plasma level being reached some two to three hours after ingestion[15]. This was the reason for administering – in this investigation as well as in another by the same author[20] – a morning dose of levodopa in a ratio of ⅔ ‹Madopar› HBS to ⅓ standard ‹Madopar› to all patients. Additional individual doses of standard ‹Madopar› were necessary in most patients for optimal results. In the authors' experience, therefore, treatment with ‹Madopar› HBS always necessitates combination with individual doses of standard ‹Madopar›.

Responses with regard to levodopa-induced dyskinesia varied after the switchover to ‹Madopar› HBS. The

severity and frequency of foot dystonia, particularly early-morning dystonia associated with off periods (off-period dystonia) showed a clear regression in all the patients affected in this trial, and similar responses were reported for biphasic dyskinesia (Table 4). Peak-dose dyskinesia, on the other hand, showed a growing tendency which necessitated withdrawal of therapy in some cases. In many patients, choreoathetotic motor restlessness, particularly marked in the afternoons, was probably an 'overlapping' effect[20] and points to a pharmacokinetic problem of the slow-release preparation used. Though the continuous-release principle of the ‹Madopar› HBS capsule is based on controlled release of levodopa and prolonged sojourn of the capsule in the stomach[7], the levodopa cannot be absorbed until it reaches the jejunum. Continuous absorption of levodopa which is released at a steady rate in the stomach would therefore depend on a steady process of gastric emptying. This requirement is not satisfied, however, since gastric emptying is not a steady process and is, in addition, dependent on many external factors such as acidity, food intake and the effect of drugs such as anticholinergics[18]. Since levodopa is absorbed very rapidly in the jejunum, abrupt increases in plasma levels of ‹Madopar› HBS may occur when a prolonged phase of gastric immobility (for instance, after a meal) is followed by resumption of peristaltic activity. Such a mechanism would at least provide a possible explanation for the clinical observation of acute afternoon dyskinesia in many of the patients in this and other studies[20].

The present study shows that, despite the unresolved shortcomings, treatment with ‹Madopar› HBS of patients with Parkinson's disease experiencing fluctuations in response is superior to standard ‹Madopar› treatment in 60% of cases over a period of up to 1.5 years.

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