A comparison of the effects of controlled-release levodopa (Madopar CR) with conventional levodopa in late Parkinson's disease

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Abstract

In this multicentre study a controlled-release formulation of levodopa and the decarboxylase inhibitor benserazide (Madopar CR) was evaluated in patients with Parkinson's disease exhibiting dose-related fluctuations in motor performance in response to conventional levodopa preparations. The effect of Madopar CR, with or without conventional levodopa/benserazide, on the proportion of time spent "on", "off" or "intermediate" was compared with that of previous conventional levodopa/decarboxylase inhibitor therapy. Evaluation of the two periods of optimum therapy was based on both patient diary data and investigator opinion. Forty seven patients completed the study but full patient diaries were available for only 37. The mean optimum total daily dosage of conventional Madopar was 820 mg taken in a mean of 6·4 doses, compared with a mean optimum daily dosage of combined Madopar CR and conventional Madopar of 1088 mg, taken in a mean of 5·2 doses. Conventional Madopar was taken in addition to Madopar CR in all but eight patients. Madopar CR was felt to be advantageous in 83% and disadvantageous in 11% of patients completing the study. Considering the 37 patients for whom diary data were available, Madopar CR therapy resulted in an increase in the mean time spent "on" (p = 0·016) and a decrease in the mean time spent "off" (p = 0·029) compared with conventional Madopar alone. Individually 25 out of 37 had an increase in "on" time and 19 out of 37 experienced a decrease in "off" time. Thus Madopar CR was found to be beneficial in a significant proportion of patients experiencing fluctuations in response to conventional levodopa.

Levodopa plus a decarboxylase inhibitor remains the most effective treatment for Parkinson's disease. However, during the course of sustained therapy with levodopa, disabling fluctuations in motor control emerge so that after five years at least 50% of patients experience fluctuations in mobility throughout the day.[1–3] Although the mechanisms underlying these changes are poorly understood the maintenance of stable plasma levodopa concentrations by means of intravenous infusions of levodopa has been shown to reduce swings in motor performance dramatically.[4–6] This recognition of the importance of steady state plasma and brain concentrations of levodopa has renewed interest in oral controlled-release preparations, which offer the possibility of a more practical means of achieving relatively stable plasma levodopa concentrations.

In comparison to the conventional levodopa/benserazide preparation, Madopar CR★ has been shown to exhibit sustained-release characteristics, that is, it gives rise to sustained plasma levodopa concentrations.[7–8] However the bioavailability of the CR form is reduced, being on average 60% that of standard Madopar so that higher doses are usually required and there is a lower, delayed peak plasma concentration of levodopa.[7–8] Clinical experience so far indicates that overall "on" time is generally increased by Madopar CR but for a number of patients there is an unacceptable delay in turning "on" when Madopar CR totally replaces conventional levodopa.[9–11] In this study we evaluated Madopar CR, with the addition of conventional levodopa if necessary, in patients with dose-related fluctuations in motor performance.

Patients and methods

A total of 87 Parkinsonian patients exhibiting fluctuations in motor performance in response to oral levodopa/decarboxylase inhibitor therapy entered the study. Since the rationale for Madopar CR is based on an association between plasma concentration and fluctuations, the protocol excluded patients with completely random "on-off" switches unrelated to timing of dosage. The mean age of the patients was 64·5 years (43·9 to 86·8 years). Disease duration ranged from 2 to 22 years (mean 10 years) and duration of levodopa therapy from 1 to 17 years (mean 8·3 years, SD 4·2 years). Eighty nine per cent of patients had a Hoehn and Yahr rating of Grade II or more and 58% had a rating of Grade III or more. The study was conducted at eight centres and was of open, sequential, comparative design. Before the study, 75 patients had been taking anti-Parkinsonian agents in addition to their levodopa therapy. These included bromocriptine (19 patients), selegiline (32 patients) and anticholinergics (17 patients). Patients were allowed to continue on these, provided the doses were kept constant throughout the study.

Phase 1 of the study involved an initial dose titration period of a suggested duration of 14 to 42 days during which the investigator adjusted conventional Madopar (levodopa/benserazide)

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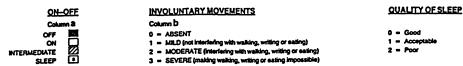Poole General Hospital, Poole
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Figure 1 Record chart (patient diary) for "on-off", involuntary movements and sleep.

RECORD CHART
FOR
"ON–OFF", INVOLUNTARY MOVEMENTS, AND SLEEP

therapy, if necessary, until optimum clinical benefit was obtained. Optimum clinical benefit was defined as that which gave maximum clinical effect and could be tolerated. Patients taking levodopa/carbidopa preparations before the study were switched to Madopar at the start of this dose titration phase. A 28 day stable assessment period followed.

In phase 2 therapy was changed to Madopar CR, starting with a dose no more than 1·5 times the patient's optimum conventional Madopar dose and supplementing the first morning dose with conventional Madopar if necessary. A second dose titration period followed during which the size and timing of Madopar CR and conventional Madopar doses could be adjusted until optimum clinical benefit was obtained. It was suggested that dose titration should be carried out slowly over a period of 14 to 42 days. This was followed by a second stable assessment period of 28 days.

Assessment was based on patient diaries and the opinion of the investigator. Patients were

asked to keep a daily record of time spent in "off", "intermediate" or "on" state, of abnormal involuntary movements during waking hours, and of their sleep quality and time spent asleep (fig 1). At the end of the study the investigator recorded optimum doses, any concomitant medications, reasons for withdrawal (if appropriate) and their opinion on the advantages or disadvantages of Madopar CR therapy in each patient.

Statistical analysis was performed only on the mean proportions of time spent "on" and "off", by subjecting the data to a two-way analysis of variance to assess treatment and centre effects and their interaction.

Results

Eighty seven patients from seven centres were entered into the trial. Following exclusion due to protocol violations (12 patients) and withdrawal (14 patients), 61 patients reached the Madopar CR phase of the study. Thereafter there were 14 withdrawals; thus 47 patients completed the study. Reasons for withdrawals are listed in table 1.

Table 1 Reasons for withdrawals

Reason	Conventional Madopar	Madopar CR
Lack of efficacy	2	10
Side-effects	2	2
Intercurrent illness	1	2
Other	9	0
Total (n = 75)	14 (18%)	14 (18%)

Optimum dosage
Four methods were used to introduce Madopar CR at the beginning of the optimisation phase:
(1) Abrupt, same dose: conventional Madopar

Table 2   Mean proportion of waking time spent "on", "off" or "intermediate" in 37 patients with evaluable diary data

	Conventional Madopar		Madopar CR	
	Mean	SE	Mean	SE
"On"	0·655	0·038	0·717	0·038
"Intermediate"	0·213	0·031	0·193	0·034
"Off"	0·132	0·028	0·090	0·022

was abruptly replaced by Madopar CR at approximately the same dose. The dose was then titrated upwards or downwards according to response and conventional Madopar was added as necessary. (2) Abrupt, higher dose: as in (1) but the initial dose of CR was higher than that for conventional Madopar. (3) Abrupt, lower dose: as in (1) but the initial dose of CR was lower than that for conventional Madopar. (4) Gradual, lower dose: Madopar CR was very gradually introduced into the regime. One daily dose of conventional was replaced by CR, generally at weekly intervals. Conventional Madopar doses were retained or added back into the regime if necessary.

Method 2 proved to be the most popular although each investigator had a preferred method. The likelihood of completing the CR titration phase was not associated with any one method.

Not surprisingly, the time taken to optimise the dosage of conventional Madopar was on average shorter than that for Madopar CR optimisation (mean values of 21 and 41 days respectively). The mean optimum daily dosage of conventional Madopar was 820 mg (range 125–2125 mg), slightly less than for Madopar CR for which the mean was 856 mg (range 125–3375 mg). However, in addition to their Madopar CR, most (39/47) patients received supplements of conventional Madopar, the mean dosage being 231 mg (range 0–1125 mg). This brought the mean total dose of Madopar (conventional + CR) during the optimum CR period to 1088 mg (range 250–3500 mg).

The use of Madopar CR only slightly reduced the number of doses taken daily; from a mean of 6·4 doses with conventional Madopar (range 2–18) to a mean of 5·2 (range 2–6) when Madopar CR was included in the regime.

Diary data
Diary data were evaluable for 37 of the 47 patients who completed the study.

Time spent "on" or "off" During optimum Madopar CR therapy the average time spent

Table 3   Adverse events reported during the study

	Conventional Madopar	Madopar CR
Dyskinesia	3	1
Nausea	1	1
Constipation	—	2
Vomiting	—	1
Hallucination	1	2
Taste perversion	—	1
Abnormal vision	—	1
Somnolence	—	1
Skin formication	1	—
Nocturnal asthma attack*	—	1
	6	11

*fatal: relationship to drug therapy remote.

"on" was increased for 25 out of the 37 patients and decreased for 12 compared with during optimum conventional therapy. Mean time "off" was decreased in 19 out of the 37, increased in seven and unchanged in the remainder during optimum CR therapy.

Analysis of variance was used to test for treatment differences over the 37 patients as a whole. Overall a larger proportion of waking time was spent "on" ($p = 0·016$) and a smaller proportion of time spent "off" ($p = 0·029$) during optimum CR therapy (table 2).

Dyskinesias There were insufficient reliable data on dyskinesias for analysis. A large proportion of patients did not understand what was meant by the term dyskinesia or were unable to grade their dyskinesia and did not enter any results. The majority of those who did record data confused tremor with dyskinesia and, in nearly all cases, the investigator judged the data to be unreliable.

Sleep quality and quantity The average duration of sleep during the two optimum treatment periods was remarkably consistent: 8·27 hours for conventional Madopar and 8·36 hours for Madopar CR. The mean rating for quality of sleep was 0·62 during optimum conventional Madopar therapy and 0·55 during optimum Madopar CR therapy (sleep was rated as 0 = good, 1 = acceptable or 2 = poor).

Investigator's opinion
Of the 47 patients who completed the study, Madopar CR was felt to be advantageous in 39 (83%), the advantages being rated as clinically significant in 36 (77%). In five (11%) patients Madopar CR was judged to be disadvantageous and in three patients this was felt to be of clinical significance. Madopar CR was found to be both advantageous and disadvantageous in 2 patients and neither advantageous nor disadvantageous in the remaining five patients. Fourteen patients reported adverse events during the study and these are listed in table 3.

Discussion
In this open, multicentre study we found that Madopar CR increased the amount of waking time spent "on" and decreased time "spent off" in a substantial proportion of patients who completed the study. Fluctuations in response were not eradicated and in this study oral controlled-release therapy was not as effective as intravenous levodopa therapy has been shown to be.[8] Nevertheless, Madopar CR was of significant clinical advantage in three quarters of those who completed the trial.

There were a large number of patient withdrawals. Half of these patients withdrew before receiving Madopar CR and this illustrates the difficulty in maintaining adequate numbers of patients in a trial of this type. However, lack of efficacy of the controlled-release formulation was the reason given for 10 of the 14 patients who withdrew during Madopar CR therapy. Four methods of dose titration were used in this study and it is likely that with more

experience in titrating the optimum dose of Madopar CR some of these patients would have remained in the trial. Some patients experience a delay in onset of effect with Madopar CR.[9-11] Because of the importance attached by patients to predictability of response,[12] it is not surprising that the optimum therapeutic regime for most patients included at least one dose of conventional Madopar, usually taken together with the first morning dose of Madopar CR.

In common with the majority of previous studies, overall dosage in the Madopar CR phase of the study was considerably higher than during the optimum therapy with standard Madopar. However, it is unlikely that improvements in condition were due simply to an increase in dosage. This would normally be accompanied by an escalation in adverse effects, which was not observed here. Furthermore this possible explanation does not take into account the reduced bioavailablity of the controlled-release form, which is on average only 60% that of standard Madopar.[8] There was a slight reduction in the number of doses taken per day when therapy was changed to Madopar CR. A significant reduction in dose frequency might have been anticipated with a controlled-release formulation, however, improved clinical response via the maintenance of stable plasma concentrations was the primary objective rather than dose reduction.

Despite the higher overall dosage the Madopar CR phase of the study was not associated with a significantly greater incidence of adverse events. In view of the lack of quantitative data it is possible that the increase in time "on" brought about by Madopar CR was accompanied by an increased incidence of dyskinesia. Although this cannot be ruled out, the absence in reporting of dyskinesia as an adverse event during Madopar CR therapy, coupled with the generally positive views of the investigators, make this unlikely.

In some studies nocturnal akinesia and overall sleep quality have been reported to be improved by Madopar CR[8 11 14] and the results of a study in which Madopar CR was taken at bedtime specifically to combat nocturnal Parkinsonian problems are encouraging.[13] In our study mean measures of sleep quality and quantity did not differ to any great extent when standard Madopar was compared with Madopar CR. However, patients are notoriously inaccurate at assessing sleep duration and it would be unwise to assume that there were no differences between the two treatments in this respect. Another possibility is that sleep problems were not a prominent feature of this group of patients, as the relatively low scores for sleep quality (corresponding to good sleep)

throughout the trial would indicate.

For a substantial number of Parkinsonian patients with dose-related fluctuations in motor performance significant clinical advantage was derived from a combination of Madopar CR and standard Madopar. The proportion of time spent "on" was increased and time "off" decreased. The main disadvantages of this therapy were that dose titration was difficult without previous experience of Madopar CR and it was not possible to predict which patients were likely to benefit.

*Madopar is a trade mark. Madopar CR was previously called Madopar HBS and is referred to by this name in some publications.

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