J Neurol (1996) 243 : 235–240

ORIGINAL COMMUNICATION

Erik C. Wolters
H. J. Marleen Tesselaar
International (NL & UK)
Sinemet CR Study Group

International (NL-UK) double-blind study of Sinemet CR and standard Sinemet (25/100) in 170 patients with fluctuating Parkinson's disease

Received: 23 July 1993
Received in revised form: 11 April 1995
Accepted: 7 August 1995

E. C. Wolters (✉)
Department of Neurology,
Vrije Universiteit, P.O. Box 7057,
1007 MB Amsterdam, The Netherlands
Fax: +31-20-5484898

H. J. M. Tesselaar
Medical Department,
Merck Sharp & Dohme-Chibret,
Haarlem, The Netherlands

International Sinemet CR Study Group
The Netherlands:
F.E.A.M. Bussemaker (Hoorn),
J.W.H.H. Dammers (Alkmaar),
J.A. Haas (Almelo),
M.W.I.M. Horstink (Nijmegen),
E.N.H. Jansen (Enschede),
J.J. Korten (Sittard),
J.P.W.F. Lakke (Groningen),
A.A.W. Op de Coul (Tilburg),
J.P.C. Peperkamp (Den Bosch),
R.A.C. Roos (Leiden),
A.W.F. Rutgers (Groningen),
C.C. Tijssen (Tilburg),
A. van der Zwan (Zwolle),
T. van Laar (Enschede),
J.A. van Leusden (Alkmaar),
J. van Rossum (Leiden),
H.B.C. Verbiest (Den Haag),
A.J. Vermeij (Eindhoven),
E.C. Wolters (Amsterdam);
UK: J. Bakheit (Glasgow),
D. Bates (Newcastle),
R. Capildeo (Romford),
J. Chand (Essex), P. Kennedy (Glasgow),
A. Lees (London), D. Park (Essex),
S. Sturman (Birmingham),
N. Turjanski (London),
A. Williams (Birmingham)

Abstract One hundred and seventy patients with fluctuating Parkinson's disease participated in an international clinical trial to compare the effects of controlled-released Sinemet 50/200 (mg carbidopa/mg levodopa; Sinemet CR) with standard Sinemet 25/100 (Sinemet STD). The study design involved an 8-week open-label titration (dose-finding) phase (STD and CR preparations given individually during weeks 1–4 and 5–8 respectively) followed by a 24-week double-blind, double-dummy (placebo) treatment period. Drug efficacy was assessed using: (a) data from patients' diaries (i.e. "on-off" periods) (b) the functional disability profile (Northwestern University Disability Scale), (c) the neurological signs and symptoms (New York University Parkinson's Disease Scale, NYUPDS), (d) global evaluations made by the patient and treating physician and (e) the patient's evaluation of sleep. The results indicate that the number of "off" periods and the total NYUPDS score decreased significantly in the patients treated with Sinemet CR compared with those treated with Sinemet STD. Furthermore, the patient's global evaluation was significantly better in the Sinemet CR group. The number of drug-related adverse experiences was similar in the two groups, and only one serious event of this nature was reported.

Key words Parkinson's disease · Motor fluctuations · Sinemet CR

Introduction

Long-term treatment of Parkinson's disease with levodopa, in combination with a peripheral dopadecarboxylase inhibitor, is limited because responsiveness to levodopa diminishes with time in most patients [12]. Predictable wearing-off periods and/or unpredictable "on-off" periods with random swings in motor functioning will occur frequently [3]. In treating the motor fluctuations reported to be associated with certain pharmacokinetic and pharmacodynamic properties of oral levodopa [8, 15], continuous intravenous infusions of levodopa have proven helpful [15].

Controlled-release preparations of levodopa have been developed to induce a sustained elevation in plasma levodopa concentrations. One such preparation of levodopa and carbidopa, Sinemet CR (50 mg carbidopa, 200 mg levodopa), has proven successful at ameliorating motor fluctuations [6, 17] and, importantly, has been shown to

be safe and as well tolerated as conventional formulations [1, 2, 4, 5, 7, 9–11, 14, 16, 18, 19]. The clinical efficacy of Sinemet CR has been found to be superior to that of the standard preparation of Sinemet (Sinemet STD; 25 mg carbidopa, 100 mg levodopa) in both open and double-blind preliminary studies [1, 2, 4, 5, 7, 10, 11, 14, 16, 18, 19].

In this international multicentre clinical trial, the efficacy and tolerability of Sinemet CR and Sinemet STD were compared in a large number of Parkinson's disease patients who suffer motor fluctuations.

Patients and methods

Patients

Patients (n = 170) aged 35–75 years, presenting with Hoehn and Yahr stage II–IV Parkinson's disease and demonstrating major clinical signs of the illness (e.g. rigidity, tremor, postural and/or gait disturbances and predictable deterioration in motor behaviour that fluctuated with levodopa treatment) were recruited from 16 Dutch and 6 British neurological departments to participate in the trial. Of these 170 patients, 149 were assigned randomly to receive Sinemet STD (n = 75) or Sinemet CR (n = 74). A total of 131 patients completed the study, 68 in the Sinemet STD group and 63 in the Sinemet CR group (see below, Safety and tolerability, for details concerning patients who discontinued the investigation). The use of concomitant anti-parkinsonism medication, including bromocriptine or selegiline, was permitted provided the dosage remained stable throughout the study and during the 3 months immediately preceding entry into the study. Patients taking permitted concomitant medication were randomized in such a way as to ensure equal distribution between the two treatment groups.

Study design

A complete physical examination and routine laboratory tests were performed before and after the study. The trial lasted 32 weeks and comprised two phases, an 8-week titration or optimal dose-finding phase followed by a 24-week double-blind phase.

During weeks 1–4 patients were titrated with Sinemet STD to achieve the optimal clinical response (i.e. determine the STD dosage that gave the best control of their Parkinsonian symptoms). During the next 4 weeks (i.e. weeks 5–8) the process was repeated using Sinemet CR.

Following the titration period, patients were randomized to 24 weeks of double-blind treatment with either Sinemet STD plus placebo Sinemet CR or Sinemet CR plus placebo Sinemet STD. Treatment began with the optimal dose from the titration period, but investigators were allowed to alter (optimize) the dosage of Sinemet STD or CR (and placebo) at their own discretion during the double-blind phase.

Drug safety and efficacy determinations, unless specified, were performed every 2 weeks in the titration phase and at 4, 8, 12 and 24 weeks into the double-blind period. Assessment of efficacy was based on the following measures: (a) data from the patient's diary (questionnaire) concerning "on-off" periods and dyskinesias (abnormal involuntary movements); (b) the functional disability profile as assessed by the Northwestern University Disability Scale (NUDS; total score ranging from 0 to 50), to evaluate daily activities such as walking, dressing, eating, feeding, hygiene and speech; (c) the neurological signs and symptoms as evaluated through the New York University Parkinson's Disease Scale (NYUPDS; five-point scale, 0–4), to determine clinical response in terms of rigidity, tremor, bradykinesia, gait and postural stability; (d) the patient's and physician's global evaluations (five- or seven-point scales) of early morning akinesia, dystonia, pain and severity of disease; (e) the patient's evaluation (four- to six-point scales) of sleep (the length of time it took to fall asleep, the number of times they woke during the night, the rating of sleep, the average score for hours of sleep and the average time for the first morning pill to take effect). Measures b–e were determined at day 0 and following each titration phase and as stated above for the double-blind period.

The number of doses per day and the daily dosage required for optimal control of motor fluctuations and other symptoms were recorded at the end of each dose-finding phase and at the end of the double-blind period.

Percentage changes, when computed, were calculated with respect to the baseline value (end of titration with Sinemet STD).

Statistical methods

Wilcoxon's signed rank test was applied to the patients' diary data and to the NUDS and NYUPDS ratings to compare the pre-study data with the findings at the end of each dose-finding phase and at weeks 4, 8, 12 and 24 of the double-blind period.

Between-group comparisons during the double-blind period were made by analysis of variance (ANOVA) on the ranks of changes from baseline (end of the first titration period, i.e. week 4), with treatment and stratum as model effects, for the following efficacy variables: number of "off" periods, number of hours of sleep, percentage of the waking day "on" and "off", NUDS and NYUPDS scores, score for patient's global evaluation, time for first morning pill to work, number of doses per day and total daily dosage. Between-group comparisons with baseline for physician's global evaluation and the three remaining questions related to sleep (how long to fall asleep, how often awake during the night and rating of sleep) were made using McCullagh's method [13].

The incidence of clinical and laboratory adverse experiences and vital signs was considered in the safety evaluation. The number of patients with adverse experiences during therapy was compared between treatment groups using Fisher's exact test.

All statistical comparisons were two-sided tests. Probability values were rounded off to two decimal places, and differences were considered statistically significant if the rounded probability value was ≤ 0.05.

Results

Safety and tolerability

During the titration period with Sinemet STD 30 patients reported at least one adverse experience, of which 25 were considered to be at least possibly related to the study drug. During the double-blind treatment period with Sinemet STD, 15 patients had at least one adverse experience and 12 of these adverse events were considered to be related to the test medication. During treatment with Sinemet CR, the number of patients with adverse experiences, 36 during titration and 28 in the double-blind phase, was significantly higher ($P < 0.05$). Of the adverse experiences during Sinemet CR treatment, 29 and 17 in the titration and the double-blind phase, respectively, were considered to be drug-related. The frequency of drug-related clinical adverse effects did not differ significantly between the two treatments.

There was only one serious drug-related clinical adverse experience (increased dyskinesia during titration of Sinemet CR). A total of 12 patients withdrew during the titration periods because of clinical adverse experiences, two during titration with Sinemet STD and 10 during titration with Sinemet CR. During the double-blind period six patients withdrew because of clinical adverse experiences: one in the Sinemet STD group and five in the Sinemet CR group. No significant difference was found between the groups with respect to the number of patients withdrawing during the titration or double-blind period due to drug-related adverse experiences.

Drug-related clinical adverse experiences were mainly related (80%) to the neuro-psychiatric and gastrointestinal systems. Dyskinesia, dystonia, headache, hallucinations and nausea and vomiting accounted for about half of the adverse experiences recorded.

Two patients in the Sinemet CR group were reported to have had an adverse experience based on laboratory results. One patient had a decreased plasma haemoglobin concentration and another had an elevated plasma platelet count, but neither event was considered to be drug-related.

During the study a total of 39 patients withdrew (21 during the open-label titration and 18 during the double-blind phase). Eighteen withdrawals were due to adverse effects, 9 to insufficient therapeutic response and 12 either to lack of compliance or through missing follow-up appointments.

Efficacy

Titration phase

The mean proportion of the day during which the patient was asleep was 32% at the end of each titration period. The mean proportion of the waking day when the patient was "on" increased significantly ($P < 0.01$) from 68% at the end of the Sinemet STD titration period to 72% at the end of the Sinemet CR titration period (Fig. 1). Correspondingly, the mean "off" time decreased from 32% to 28% ($P < 0.01$). The mean number of "off" periods per day decreased significantly ($P < 0.01$) from four at the end of the Sinemet STD titration period to three at the end of the Sinemet CR titration period (Fig. 2).

The mean total NUDS score decreased significantly ($P < 0.01$): (a) from 10.7 in the pre-study assessment (STD 0) to 10.2 at the end of the Sinemet STD titration period and (b) from 10.2 at the end of the Sinemet STD titration period to 9.7 at the end of the Sinemet CR titration period (Fig. 3).

The mean total NYUPDS score also decreased significantly ($P < 0.01$): from 8.0 at STD 0 to 7.0 at the end of the Sinemet STD titration period, and then again from 7.0 to 6.3 at the end of the Sinemet CR titration period (Fig. 4).

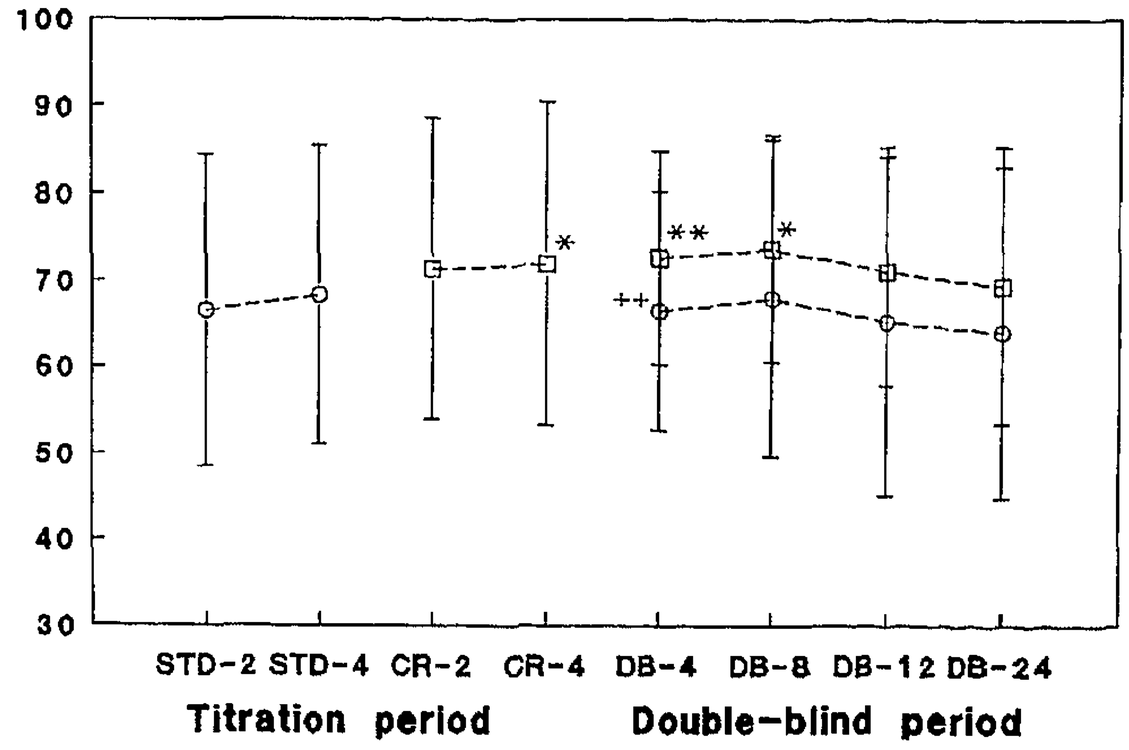

Fig. 1 Mean percentage of "on" time during open titration (n = 131) with standard Sinemet 25/100 (*STD*; *circles*; day 0–week 4) and controlled-release Sinemet 50/200 (*CR*; *squares*; weeks 4–8) and during 24 weeks of double-blind treatment (DB) with Sinemet STD (n = 68) and Sinemet CR (n = 63). * $P < 0.01$ compared with STD-4 (baseline), ** $P < 0.05$ compared with STD-4, ++ Sinemet CR significantly different from Sinemet STD at same time in double-blind period ($P < 0.05$)

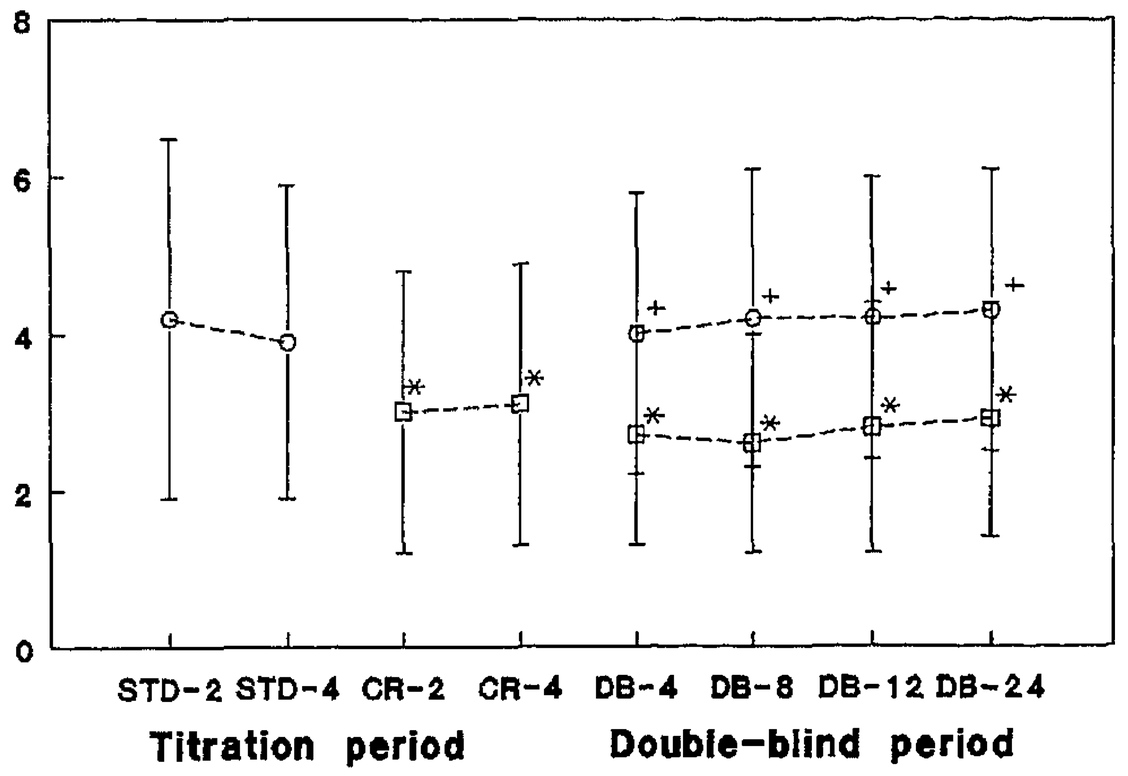

Fig. 2 Mean number of "off" periods during open titration (n = 131) with Sinemet STD (*circles*; day 0–week 4) and Sinemet CR (*squares*; week 4–8) and during 24 weeks of double-blind treatment with Sinemet STD (n = 68) and Sinemet CR (n = 63). * $P < 0.01$ compared with STD-4 (baseline), + Sinemet CR significantly different from Sinemet STD at same time in double-blind period ($P < 0.01$)

The time needed to fall asleep, the number of "wake-ups" and the total time asleep did not change significantly during the two titration periods. However, the proportion of patients who rated their sleep as very good increased from 7% in the pre-study period to 11% at the end of the Sinemet STD titration period and to 15% at the end of the Sinemet CR titration period.

The mean time for the first morning pill to take effect increased from less than 30 min at the end of the Sinemet STD period to 30–60 min at the end of the Sinemet CR period.

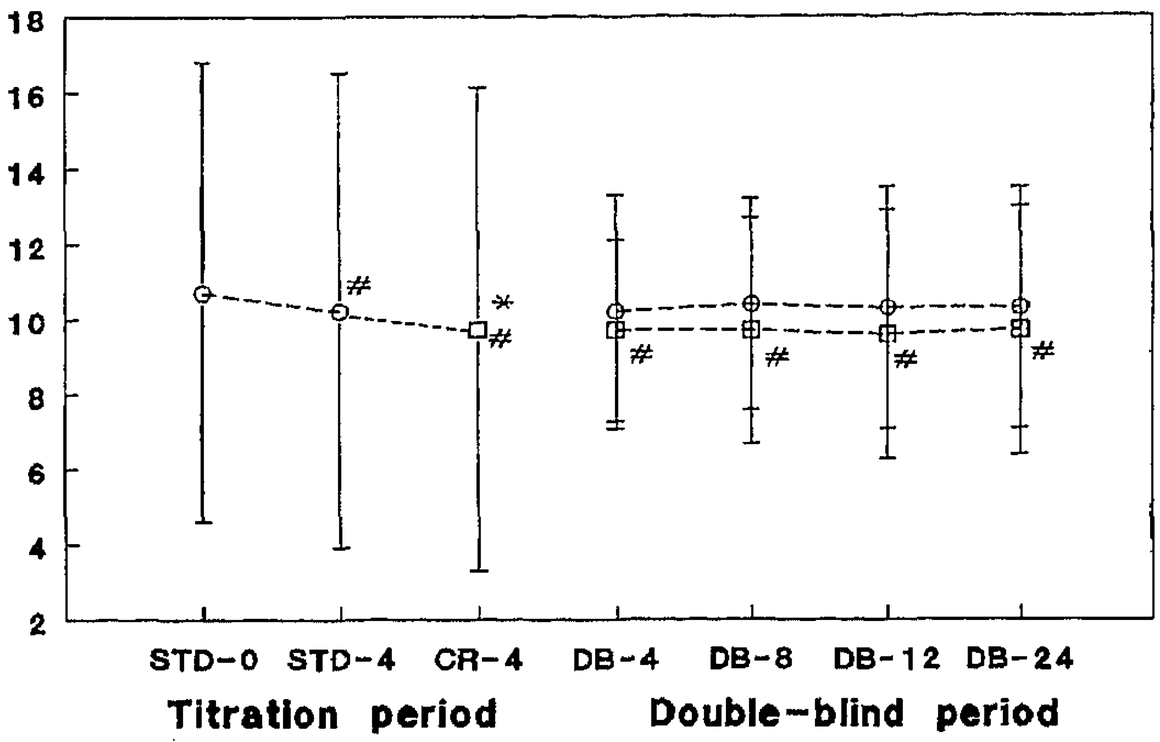

Fig. 3 Mean North-Western University Disability Scale score during open titration (n = 131) with Sinemet STD (*circles*; day 0–week 4) and Sinemet CR (*squares*; week 4–8) and during 24 weeks of double-blind treatment with Sinemet STD (n = 68) and Sinemet CR (n = 63). # $P < 0.01$ compared with STD-0 (pre-study), * $P < 0.01$ compared with STD-4 (baseline)

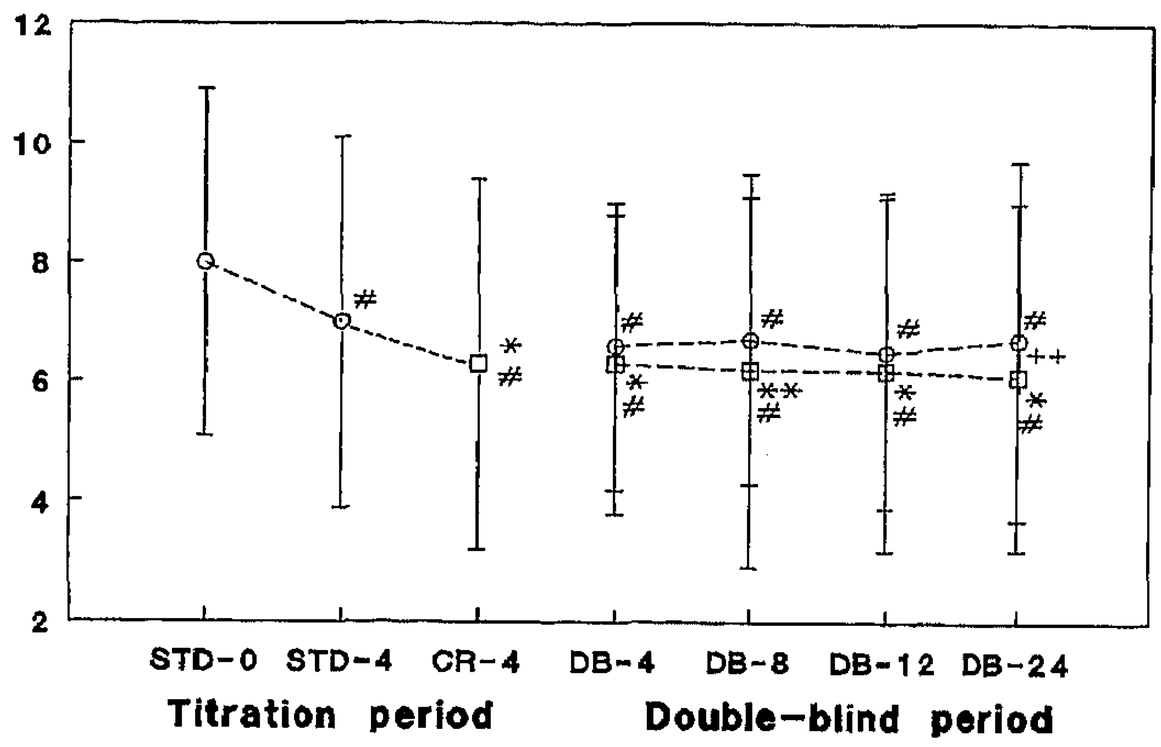

Fig. 4 Mean New York University Parkinson's Disease Scale score during open titration (n = 131) with Sinemet STD (*circles*; day 0–week 4) and Sinemet CR (*squares*; week 4–8) and during 24 weeks of double-blind treatment with Sinemet STD (n = 68) and Sinemet CR (n = 63). # $P < 0.01$ compared with STD-0 (pre-study), * $P < 0.01$ compared with STD-4 (baseline), ** $P < 0.05$ compared with STD-4, ++ Sinemet CR significantly different from Sinemet STD at same time in double-blind period ($P < 0.05$)

The number of doses per day at the end of the titration period with Sinemet CR was approximately 70% of the doses recorded after Sinemet STD titration. However the Sinemet CR tablets contained twice the dosage of levodopa compared with Sinemet STD tablets and hence the total daily levodopa dose at the end of the Sinemet CR treatment was about 130% of the dose at the end of the Sinemet STD treatment.

Double-blind phase

As mentioned previously, "baseline" refers to the end of Sinemet STD titration (i.e. STD 4). At baseline, patient slept on average 32% of the day in both treatment groups. After 24 weeks of treatment small changes in proportion of the day spent sleeping were found in the two groups: –1% for Sinemet STD and +1% for Sinemet CR (n.s.). The mean proportion of the waking day when a patient was "on" averaged 68% at baseline and 64% after 24 weeks of treatment in the Sinemet STD group (n.s.). In the Sinemet CR group the mean proportion of "on" time (68% at baseline) increased significantly to 73% at week 4 ($P < 0.05$) and to 74% at week 8 ($P < 0.01$), but waned to 69% by the end of the study (see Fig. 1). A significant difference ($P < 0.05$) between the two treatments was revealed during the double-blind period only at week 4, when percentage "on" time was significantly greater in the Sinemet CR group.

The mean daily number of "off" periods was four in both treatment groups at baseline. In the Sinemet STD group the mean number of "off" periods did not change significantly during the double-blind phase. However, in the Sinemet CR group a significant decrease ($P < 0.01$) of almost one "off" period was observed at all assessment times in the double-blind period (Fig. 2). Furthermore, there were significantly fewer "off" periods ($P < 0.01$) in the Sinemet CR than in the Sinemet STD group at all assessment times in the double-blind phase.

The mean baseline NUDS score was close to 10 in both treatment groups. During double-blind treatment neither the Sinemet STD nor the Sinemet CR group demonstrated significant changes in NUDS score (Fig. 3).

For the mean total NYUPDS score a non-significant decreasing trend was seen during double-blind treatment in the Sinemet STD group, whereas a significant decrease ($P < 0.01$) of almost 1 was observed in the Sinemet CR group (Fig. 4). This reduction in NYUPDS score in the Sinemet CR group was mainly due to amelioration of rigidity, tremor and bradykinesia, not to improvement in gait and postural stability. Comparing the two medications in the double-blind period, the reduction in NYUPDS score with Sinemet CR was significantly greater ($P < 0.05$) than that achieved with Sinemet STD after 6 months' treatment.

During the double-blind treatment period no significant within- or between-group (treatment) changes were detected in the distribution of answers for any of the questions related to the evaluation of sleep. Baseline scores for hours of sleep, at approximately 4.5 (on a six-point scale), were equal in both groups (a score of 4 refers to 4–6 h sleep, a score of 5, to 6–8 h sleep). Mean changes in the sleep score were small in both groups (on average an increase of 0.2). The difference was significant ($P < 0.05$) at all evaluation times only in the Sinemet CR group. How-

ever, the difference between treatments was not significant at any time in the double-blind period.

The mean baseline score for time for the first pill to take effect was 2.0 in both groups (the scores ranged from 1 to 4, with 1 = < 30 min, 2 = 30–60 min, 3 = 60–90 min and 4 = > 90 min). Mean changes were small in the Sinemet STD group but significant ($P < 0.01$) at each evaluation in the Sinemet CR group. Consequently, Sinemet CR took significantly more time to take effect than the Sinemet STD preparation throughout the double-blind period. For example, the mean score at the end of the study was 2.6 in the Sinemet CR group versus 2.1 in the Sinemet STD patients ($P < 0.01$).

A score of 2 in the patient's global evaluation implies that the patient feels better than at baseline, whereas a score of 3 implies that the patient feels the same as at baseline. In the Sinemet STD group, the mean score at week 24 was 3.1, while that in the Sinemet CR group was 2.9. There was a significant difference in the patient's global evaluation between the treatment groups in favour of Sinemet CR at weeks 12 ($P < 0.05$) and 24 ($P < 0.05$). When considering the physician's global evaluation, however, no significant difference between the two groups was found at any time.

In both treatment groups during the double-blind period, there was a significant decrease in the mean number of doses per day relative to the end of titration with Sinemet STD. In the Sinemet STD group the number decreased from 5.7 to 5.1 ($P < 0.01$), in the Sinemet CR group from 5.8 to 4.9 ($P < 0.01$).

Discussion

The principal findings in 131 patients with dose-related motor fluctuations in Parkinson's disease were the following:

a) In both the open (titration) and double-blind phases, Sinemet CR, but not Sinemet STD, produced significant beneficial changes in the mean percentage "on" time and the number of "off" periods.

b) The number of "off" periods during the open and the double-blind phases was significantly lower with Sinemet CR than with Sinemet STD.

c) Sinemet CR tended to produce better NUDS scores than Sinemet STD and produced significantly better NYUPDS values.

d) The patient's global evaluation was better with Sinemet CR than with Sinemet STD during the double-blind treatment.

e) The safety and tolerability of Sinemet CR and Sinemet STD were similar.

The increased clinical efficacy, as measured with NYUPDS and NUDS, in the Sinemet CR patients implies that intracerebral dopamine concentrations were elevated in these patients. However, this conclusion is untenable when taking into account the calculated bioavailability of levodopa in both groups. Although a 30% higher levodopa dosage was administered with Sinemet CR than with Sinemet STD, this higher Sinemet CR dosage required for control of parkinsonian symptoms is partly accounted for by its lower bioavailability (71%) [19]. The calculated mean difference in daily levodopa dosage between Sinemet STD and Sinemet CR was only 80 mg. Incomplete absorption (incomplete disintegration of the polymer matrix), as well as increased first-pass decarboxylation due to slow drug release, may be responsible for the decreased bioavailability of Sinemet CR [19]. The higher efficacy may be attributable to the more stable levodopa plasma concentrations.

Considered separately, the symptoms dealt with in the NYUPDS showed clinical improvement in the CR group, especially in the degree of rigidity and bradykinesia, but not in gait and postural instability. This pattern suggests the involvement of levodopa, which is known to ameliorate rigidity and bradykinesia rather than gait and postural stability. In previous work, plasma levodopa concentrations in patients given Sinemet CR fluctuated less as a result of a lower plasma peak and a higher end-of-dose titre [6, 19]. The CR formulation thus ensures more "economic" treatment by avoiding "off" periods induced by insufficient end-of-dose concentrations.

The number of doses per day in the Sinemet CR group decreased significantly, by 30% from 5.7 to 4.1, during the 4-week open titration period. Although the difference grew smaller during the 24-week double-blind period, the daily dose of Sinemet CR at the end of the study was still significantly lower (by 15%, 4.9 doses/day). Sinemet CR therapy, therefore, not only stabilizes plasma levodopa concentrations but also results in prolonged levodopa activity, which is more practical and convenient for the patient.

The prolonged and stabilizing effects of Sinemet CR are also reflected by the "on" and "off" scores. Moreover, dystonia was found to be improved more in the CR than in the STD group (levodopa-induced dystonia generally occurs as an end-of-dose phenomenon, and its amelioration should correspond to an increase in "on" time).

The improvement in clinical efficacy was not obtained at the expense of an increase in drug-related adverse effects in the participating patients; adverse events were seen equally in the Sinemet STD and Sinemet CR groups and consisted mainly of gastrointestinal and neuropsychiatric complaints.

Patients reported a delayed response to Sinemet CR compared with Sinemet STD. It was observed that patients who broke their CR tablets in half for the first morning dose seemed to suffer less from this problem. Increasing the surface area by breaking the tablet may have promoted faster dissolution and absorption, leading to an earlier rise to peak plasma levodopa concentrations [11].

Increase in dyskinesia during Sinemet CR treatment was noted in the more seriously affected patients, possibly due to their narrower therapeutic window. The occurrence of dyskinesia appeared to depend on circumstances and disease factors rather than on the levodopa formulation. This is consistent with the findings of previous studies [6, 16, 18].

This study demonstrated that Sinemet CR had greater clinically beneficial effects than Sinemet STD on "off" periods, NUDS score and patient's global evaluation during both the open-label titration phase and the 24-week double-blind treatment period. These benefits were not achieved at the expense of safety and/or tolerability, and the amount of total daily bioavailable levodopa was not greater.

References

1. Bush DF, Liss CL, Morton A, Sinemet CR Multicenter Study Group (1989) An open multicenter long-term treatment evaluation of Sinemet CR. Neurology 39 [Suppl 2]:101–104
2. Deleu D, Jacques M, Michotte Y, Ebinger G (1989) Controlled-release carbidopa/levodopa (CR) in Parkinsonian patients with response fluctuations on standard levodopa treatment: clinical and pharmacokinetic observations. Neurology 39 [Suppl 2]:88–92
3. Fahn S (1974) "On-off" phenomenon with levodopa therapy in parkinsonism. Neurology 24:431–441
4. Feldman RG, Mosbach PA, Kelly MR, Thomas CA, Saint Hilaire MH (1989) Double-blind comparison of standard Sinemet and Sinemet CR in patients with mild-to-moderate Parkinson's disease. Neurology 39 [Suppl 2]:96–101
5. Friedman JH (1988) An open trial of continuous release carbidopa/l-dopa (Sinemet CR) for the treatment of mild to moderate Parkinson's disease. Neurology 38 [Suppl 1]:180
6. Goetz CG, Tanner CM, Klawans HL, et al (1987) Parkinson's disease and motor fluctuations: long acting carbidopa/levodopa (CR4-Sinemet). Neurology 37:837–878
7. Goetz CG, Tanner CM, Shannon KM, et al (1988) Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. Neurology 38:1143–1146
8. Hardie RJ, Lees AJ, Stern GM (1984) On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study. Brain 107:487–506
9. Hutton JT, Morris JL (1991) Long-term evaluation of Sinemet CR in parkinsonian patients with motor fluctuations. Can J Neurol Sci 18:467–471
10. Hutton JT, Morris JL, Gustavo CR, et al (1988) Treatment of chronic Parkinson's disease with controlled-release carbidopa/levodopa. Neurology 45: 861–864
11. Hutton JT, Morris JL, Bush DF, Smith ME, Liss CL, Reines S (1989) Multicenter controlled study of Sinemet CR vs Sinemet (25/100) in advanced Parkinson's disease. Neurology 39 [Suppl 2]:67–72
12. Marsden CD, Parkes JD (1977) Success and problems of long-term levodopa therapy in Parkinson's disease. Lancet 1: 345–349
13. McCullagh P (1980) Regression models for ordinal date. IRSS [B] 42: 109–142
14. Pfeiffer RF, Wilken KE, Glaeske C (1988) Sinemet CR4 in Parkinson's disease. Neurology 38 [Suppl 1]:419
15. Quinn N, Parkes JD, Marsden CD (1984) Control of on/off phenomenon by continuous intravenous infusion of levodopa. Neurology 34:1131–1136
16. Rondot P, Ziegler M, Aymard N, Teinturier A (1989) Effect of controlled-release carbidopa/levodopa on motor performance in advanced Parkinson's disease. Neurology 39 [Suppl 2]: 74–77
17. Sage JI, Mark MH (1988) Comparison of controlled-release Sinemet (CR4) and standard Sinemet (25/100) in advanced Parkinson's disease: a double-blind cross-over study. Clin Neuropharmacol 11:174–179
18. Wolters EC, Horstink MWIM, Roos RAC, Jansen ENH (1992) Superior clinical efficacy of Sinemet CR 50/200 versus Sinemet 25/100 in patients with fluctuating Parkinson's disease. Adv Neurol 60:648–652
19. Yeh KC, August TF, Bush DF, et al (1989) Pharmacokinetics and bioavailability of Sinemet CR: summary of human studies. Neurology 39 [Suppl 2]: 25–38