Long-Term Evaluation of Sinemet® CR in Parkinsonian Patients with Motor Fluctuations

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ABSTRACT: The safety and efficacy of Sinemet® CR, a controlled-release formulation of carbidopa/levodopa, were investigated in a three year, open-label trial involving 18 parkinsonian patients with fluctuating motor response. The average daily levodopa dosing frequency did not change significantly during long-term treatment. Efficacy measures generally revealed a gradual progression of parkinsonian disability. Patient diaries of motor fluctuations revealed relative stability of time "on" but with a tendency toward increased time "on with dyskinesias" over the 36 month follow-up period. There were no adverse laboratory results deemed to be related to Sinemet® CR and no unexpected side effects were observed.

RÉSUMÉ: Évaluation du Sinemet® CR à long terme chez les patients parkinsoniens qui ont des fluctuations motrices La sécurité et l'efficacité du Sinemet® CR, une formule à libération contrôlée de carbidopa/lévodopa, ont été investiguées par une étude ouverte de trois ans impliquant 18 parkinsoniens ayant des fluctuations de la réponse motrice. La fréquence moyenne quotidienne de la prise de lévodopa n'a pas changé significativement pendant le traitement à long terme. Les mesures d'efficacité ont généralement révélé une progression graduelle de l'invalidité parkinsonienne. Le journal des fluctuations motrices tenu par chaque patient a montré une stabilité relative de la durée des périodes "on", avec une tendance vers un allongement des périodes "on" acconpagnées de dyskinésies sur un suivi de 36 mois. Aucune altération des résultats de laboratoire n'a été jugée comme étant reliée à la prise de Sinemet® CR et aucun effet secondaire inattendu n'a été observé.

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The combination of levodopa and a peripheral dopa decarboxylase inhibitor (carbidopa or benserazide) continues to be the mainstay for the treatment of Parkinson's disease. It provides stable, effective relief of parkinsonian symptoms for several years in most patients. Unfortunately, prolonged use often is associated with fluctuations in therapeutic response.[1] Fluctuating response to levodopa usually begins with "wearing-off", in which the length of therapeutic benefit derived from a single dose gradually diminishes, and may progress to rapid oscillating between periods of good mobility and relative immobility ("on-off" phenomenon) and dyskinesias. Approximately 50% of patients treated with levodopa for five years can be expected to develop response fluctuations.[2]

Management of response fluctuations is the greatest single challenge to the long-term treatment of advanced parkinsonian patients. More frequent administration of smaller individual doses of levodopa maintains more stable plasma levodopa levels and is typically used to mitigate motor fluctuations. Continuous intravenous[3-6] and intraduodenal or intrajejunal[7-9] infusions of levodopa have been shown to attenuate response fluctuations substantially. While neither of these are practical routes of levodopa administration for most patients, it seems clear from these observations that response fluctuations must be attributable, at least in part, to oscillating plasma levodopa levels.[10]

An orally administered preparation providing more stable, sustained plasma levodopa levels compared to the currently marketed short acting preparations would be a preferable approach for the majority of parkinsonian patients with fluctuating response. The first three controlled-release carbidopa/levodopa preparations to undergo clinical testing produced unsatisfactory or equivocal results.[11-14] Sinemet® CR (designated Sinemet® CR-4 is some previous reports) contains 50 mg of carbidopa and 200 mg of levodopa in a slowly eroding matrix that gradually releases the active compounds. In vivo absorption of levodopa from Sinemet® CR has been shown to be continuous for 4 to 5 hours.[15] Open-label and double-blind studies have shown that Sinemet® CR is tolerated as well as standard Sinemet® with significantly fewer daily doses.[16-22] A multi-center controlled trial with a 16 week double-blind crossover phase demonstrated that Sinemet® CR was as safe and well tolerated

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as the standard preparation, significantly reduced daily "off" time, was preferred by patients by approximately a two-to-one ratio, and required an average 33% fewer daily doses.[23]

The safety and efficacy of Sinemet® CR have been well documented, however, the majority of studies reported have been of brief duration. Relatively little is known of the effects of long-term use of this new preparation. Three open-label studies reported Sinemet® CR to be efficacious and well tolerated for up to 12 months.[24-26] A two year study comparing 12 patients on Sinemet® CR with 12 matched patients on standard Sinemet® found increased "on" time and fewer side effects associated with Sinemet® CR.[27] An open-label study of eight patients reported Sinemet® CR to be well tolerated, with good maintenance of daily "on" time, for a period of 36-39 months.[28] We report now on our long-term experience with Sinemet® CR in parkinsonian patients with motor response fluctuations.

Methods

Subjects

Following participation in the multi-center controlled trial of Sinemet® CR mentioned above, 18 patients (15 men and 3 women) from our site elected to continue using the new formulation on an open-label basis. The mean age of the patients was 67.4 years and the mean duration of Parkinson's disease was 10.5 years. Ten patients were categorized as Hoehn & Yahr Stage II, four as Stage III, and four as Stage IV. All patients had previously required standard Sinemet® at least four times daily and all had complaints of fluctuating motor response averaging 2.8 years in duration. No patients were receiving amantadine, monoamine oxidase inhibitors, or dopamine agonists upon study entry, however, these agents were added to the medication regimen as needed during the three year course of the long-term extension study. In some cases, Sinemet® CR was augmented by small doses of standard Sinemet® during long-term treatment.

Procedures

Patients were switched from Sinemet® 25/100 to Sinemet® CR and titrated to optimal level of function over a four week baseline period. The initial daily dosage of levodopa with Sinemet® CR was 100% to 120% of the total daily levodopa required with standard Sinemet®, and the initial number of daily doses of Sinemet® CR was 50% to 75% of the daily doses of standard Sinemet®. Patients visited the clinic for clinical observation and dosage adjustment at weeks 1, 2, and 4 of the baseline period. (All patients then entered a 16 week double-blind crossover study of Sinemet® CR compared to Sinemet® 25/100 as part of the multicenter trial described elsewhere).[23] Upon conclusion of the double-blind crossover phase, all patients were returned to their optimal regimen of Sinemet® CR for the long-term extension study described here.

Patients visited the clinic for observations at 1 and 3 months following the baseline period, quarterly through month 18, and semi-annually through month 36. The Unified Parkinson's Disease Rating Scale (UPDS) was completed on day 1, week 2, and week 4 of the Sinemet® CR baseline and at each clinic visit through long-term extension month 30. Patients were given two scores on the Activities of Daily Living section, one for when they were "on" (good motor function), and one for when they were "off" (relatively immobile). Other efficacy measures included the Schwab & England Activities of Daily Living Scale ("on" and "off") and Hoehn & Yahr staging of parkinsonism.

Patients kept a diary of their global motor functioning for two nonconsecutive days of the week prior to a clinic visit. For each hour of the day that a diary was kept, patients recorded whether they were asleep, had good motor function ("on"), good motor function but with involuntary movements ("on with dyskinesias"), or poor motor function ("off").

Vital signs were recorded and adverse experiences were monitored at each clinic visit throughout the study. Laboratory tests including CBC, SMA-12, and urinalysis were performed at the beginning of the long-term extension, at each follow-up visit for the first year, and once a year thereafter. Electrocardiography was completed at the end of the baseline period and at months 18 and 30 of the long-term phase.

Results

Average daily levodopa, dosing frequency, efficacy evaluation scores, and global motor functioning information from patient diaries were analyzed by correlated t tests. The percentage of waking hours "on", "on with dyskinesias", and "off" were calculated from patient diaries for statistical analysis. It should be noted that higher scores on the UPDS indicate poorer functioning. Efficacy assessments were completed on 13 patients through month 30 and were then discontinued. Levodopa dosing data were complete for 12 patients and diaries of motor functioning were kept by 8 patients through long-term month 36.

Patient Withdrawals

A total of five patients withdrew from this long-term study. Four patients died, all for reasons unrelated to the use of the study drug, and one patient relocated to another city and was lost to follow-up.

Levodopa Dosage and Dosing Frequency

The average daily dosing frequency and average daily intake of levodopa for week 4 of the Sinemet® CR baseline through the long-term extension (either as Sinemet® CR or Sinemet® 25/100) are shown in Figure 1. The average dosing frequency of Sinemet® CR increased from 3.42 doses/day at baseline to 4.0 doses/day at long-term month 36. When standard Sinemet® is included, the average daily dosing frequency increased to 4.33 doses/day at month 36. These differences are not statistically significant. Average daily levodopa intake as Sinemet® CR decreased significantly ($p < .01$) from baseline (mean = 1083 mg/day) to long-term month 36 (mean = 800 mg/day). The decrease in daily levodopa intake remains significant ($p < .01$) when levodopa from standard Sinemet® is included at month 36 (mean = 833 mg/day).

Of the patients with complete data through month 36, a total of 6 patients augmented Sinemet® CR with standard Sinemet® 25/100 at some time during the study. Typically this involved taking a single Sinemet® 25/100 upon arising in the morning for a quick "boost" while waiting for the first dose of Sinemet® CR to take effect. One patient used it only briefly during the first 6 months; two between month 6 and month 18; and three used it for the majority of the long-term follow-up.

The significant reduction in average daily levodopa intake over the course of this study is not unexpected. The amount of Sinemet® CR per dose was decreased for some patients as dose-

related side effects of levodopa, primarily dyskinesias, became increasingly problematic. Frequently, the reduction in levodopa was accompanied by the addition of a dopaminergic agonist or MAO-B inhibitor to the patient's medication regimen. These agents were not being used by any patients at month 6, whereas, 5 of 12 patients were using one or more of them by month 36.

Efficacy

UPDS scores for the 13 patients with complete data tend toward a general progression in disability. Scores from the Activities of Daily Living section (Figure 2) deteriorated significantly, both when patients were "on" (baseline mean = 7.77; month 30 mean = 13.08; $p < .005$) and when they were "off" (baseline mean = 14.08; month 30 mean = 20.08; $p < .01$). Mood/Mentation scores also worsened significantly (baseline mean = 2.77; month 30 mean = 4.54; $p < .05$). There were no significant changes in Motor Exam (baseline mean = 12.46; month 30 mean = 14.23) or Complications of Therapy scores (baseline mean = 4.92; month 30 mean = 5.46).

Schwab and England Activities of Daily Living scores declined significantly over the long-term, both when patients were rated "on" (baseline mean = 84.62%; month 30 mean = 75.39%; $p < .001$) and when they were rated "off" (baseline mean = 71.54%; month 30 mean = 56.92%; $p < .01$). The average Hoehn and Yahr stage of parkinsonism did not change significantly (baseline mean = 2.54; month 30 mean = 2.77).

The patient diaries of global motor functioning provide the most direct information regarding motor response fluctuations. The ratios of waking hours "on", "on with dyskinesias", and "off" have remained quite stable over time (Figure 3; The month 30 ratio of average time "on" and "off" is somewhat inaccurate due to one patient reporting that he was uncharacteristically "off" for an entire day as a result of a gastrointestinal malabsorption syndrome). There were no significant differences in percentages of waking hours "on" (baseline mean = 82.88%; month 36 mean = 78.79%), "on with dyskinesias" (baseline

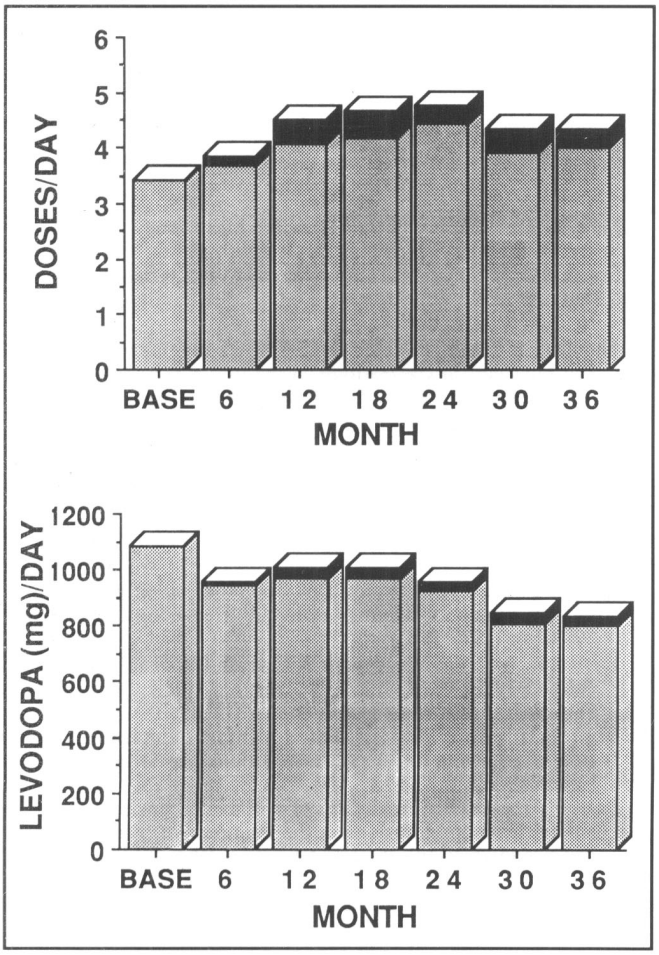

Figure 1 — Mean number of daily doses of levodopa (top) and mean daily levodopa intake (bottom) for 12 patients from baseline through 36 months of treatment with Sinemet® CR. Sinemet® CR treatment was augmented by standard Sinemet® in some cases. Solid shading indicates levodopa given as standard Sinemet® and hatched shading indicates levodopa given as Sinemet® CR.

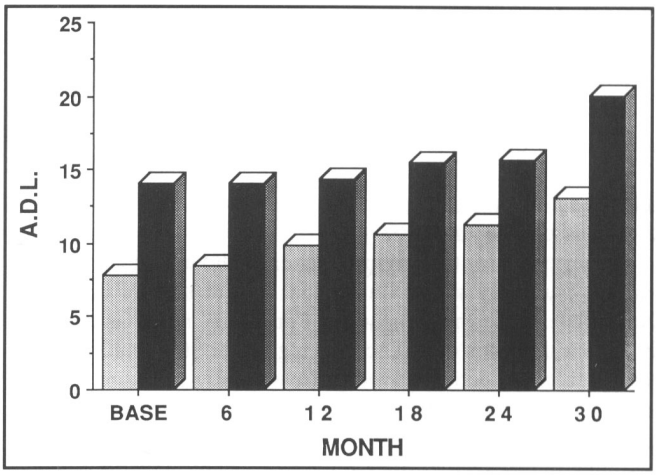

Figure 2 — UPDS Activities of Daily Living Scores for 13 patients from baseline through 30 months of treatment with Sinemet® CR. Patients were scored for both "on" (hatched shading) and "off" (solid shading) motor functioning. Lower scores represent better functioning.

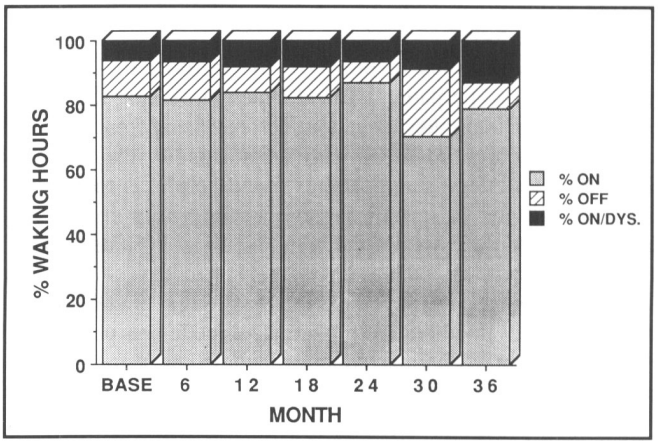

Figure 3 — Percentage of waking hours "on", "off", and "on with dyskinesias" reported in 8 patients' diaries from baseline through 36 months of treatment with Sinemet® CR. The month 30 ratio of time "on" and "off" is somewhat inaccurate due to one patient reporting that he was uncharacteristically "off" for an entire day due to a gastrointestinal malabsorption syndrome.

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mean = 6.00%; month 36 mean = 13.24%), or "off" (baseline mean = 11.13%; month 36 mean = 7.97%). Though not statistically significant, it is noteworthy that there was less time "off" reported at month 36 compared to the baseline period.

Safety Profile

There were only 4 adverse experiences thought to be related to use of the study drug. One patient was hospitalized for a confusional episode after he accidentally ingested too much Sinemet® CR. This was the only adverse experience deemed "serious". A second patient also experienced a confusional episode after taking more Sinemet® CR than had been prescribed. One patient had orthostatic hypotension which improved with increased fluid and salt intake, and another patient had increased dyskinesias at the month 36 visit. No adverse laboratory reports were deemed to be related to the study drug and no new side effects were observed.

Discussion

The results of this study demonstrate the long-term safety and efficacy of Sinemet® CR in parkinsonian patients with fluctuating motor response. There were no unexpected side effects and the safety profile is comparable to that of standard Sinemet® for a period of at least three years.

As expected for the group of patients studied, efficacy observations generally showed a gradual progression of disability. Nevertheless, the maintenance of "on"/"off" ratios as recorded in patient diaries is quite encouraging. After 36 months of long-term treatment, patients averaged essentially the same amount of daily time "on" as they did during the baseline. The relative stability of "on" time versus "off" time is likely attributable to a combination of factors, including more stable levodopa levels secondary to Sinemet® CR, careful follow-up, and augmentation by dopamine agonists and an MAO-B inhibitor. The section of the UPDS relating to Complications of Therapy (e.g., fluctuations, dyskinesias) showed very little change over time. Although the sample size is admittedly rather small, these data indicate that motor response fluctuations may not have progressed as rapidly as would have been expected with standard carbidopa/levodopa.

Due to the delayed response to the initial daily dose of Sinemet® CR, some patients found benefit in taking their first morning dose 30 minutes to an hour before arising from bed and others supplemented the initial daily dose with standard Sinemet®. A strategy some patients found helpful is to break a Sinemet® CR tablet in half for the first morning dose. This increases the surface area of the tablet by about 30% and accelerates absorption.

The pathogenesis of levodopa-induced motor fluctuations is complex, likely involving both pharmacokinetic and pharmacodynamic factors.[29] Pharmacokinetics include peripheral absorption, levodopa conversion to dopamine, and central dopamine storage.[5] Pharmacodynamic factors determine the regulation or sensitivity of dopaminergic receptors.[30] Levodopa itself may not exert a toxic effect on the nigrastriatal system, however, it is becoming clear that chronic intermittent delivery of levodopa, through the use of short-acting oral preparations, may alter the responsiveness of dopamine receptors that likely operate tonically in normal systems.[31] Receptors down-regulated through long-term pulsatile delivery may be partially restored through continuous administration of levodopa.[32] Sinemet® CR cannot be expected to produce plasma levodopa profiles comparable to continuous infusion. Nevertheless, compared to standard Sinemet®, it does provide more sustained plasma levodopa levels[15] with significantly fewer doses per day.[23] Any improvement over the intermittent, pulsatile nature of levodopa delivered through short-acting formulations should provide smoother striatal response.

While Sinemet® CR certainly does not eliminate motor response fluctuations, we believe that it offers significant benefit compared to standard carbidopa/levodopa for advanced parkinsonians with fluctuating motor response. It appears that progression of fluctuations may be slowed somewhat. The reduced dosing frequency is certainly more convenient and may well aid in patient compliance. The overall clinical control of advanced parkinsonians may be enhanced in some by augmentation with standard Sinemet®, dopamine agonist agents, or MAO-B inhibitors. In our experience, Sinemet® CR is a potent and well tolerated medication that is the drug of choice for most advanced parkinsonians.

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