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An open-label evaluation of the tolerability and safety of Stalevo® (carbidopa, levodopa and entacapone) in Parkinson's disease patients experiencing wearing-off

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Summary. *Objectives*: To evaluate the tolerability, safety and efficacy of Stalevo® (carbidopa, levodopa and entacapone) in Parkinson's disease (PD). *Background*: Levodopa provides the most effective symptom control for the treatment of Parkinson's disease (PD). However, its long-term use is limited by the development of motor complications such as wearing-off. Catechol-O-methyltransferase (COMT) inhibitors such as entacapone extend the plasma half-life of levodopa and reduce 'off' time. Stalevo is a new levodopa product that combines carbidopa, levodopa and entacapone in one tablet. Clinical studies have not been reported with this compound. *Design methods*: An open-label, multi-center US trial evaluated 169 consecutive PD patients experiencing end-of-dose wearing-off, with ($n = 39$) and without ($n = 130$) mild dyskinesia. Patients were switched from immediate-release carbidopa/levodopa to Stalevo and were treated for four weeks. Assessments included tolerability measures, adverse events profile, the disease-specific quality of life instrument PDQ-39, UPDRS parts II, III, and question 39 and investigator and patient global clinical assessments. *Results*: 14 subjects (8%) discontinued treatment with Stalevo, of which 12 (7%) were due to adverse events. 11/130 (8.5%) subjects developed new onset dyskinesia and 17/39 (43.6%) of patients with existing dyskinesia reported a worsening in their dyskinesia. However, this was managed by a change in dose in 21.4% of patients and in another 10.7% dyskinesias resolved without any need for dose adjustment. Other side effects were infrequent and mild, the most common being nausea (12.4%) dizziness (6.5%) and somnolence (6.5%). Stalevo treatment resulted in significant improvements in PDQ-39

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and UPDRS (II + III) scores ($p < 0.001$). Assessment of 'off' time demonstrated a reduction in off time in 32% of patients, compared with an increase in 7% of patients. Improvements were noted by both investigator (68.1%) and patient (68.6%) assessments. *Conclusions*: Switching PD patients experiencing wearing-off from carbidopa/levodopa therapy to Stalevo was safe, well tolerated and resulted in clinical improvement.

Keywords: Parkinson's disease, levodopa, Stalevo, COMT inhibition, tolerability.

Introduction

Since its introduction, levodopa has remained the mainstay of therapy for Parkinson's disease (PD) as it provides the most effective symptomatic control of parkinsonian symptoms (Agid, 1999; Lees, 2002). Although a number of novel therapies have been developed for the management of PD, virtually all patients will require levodopa therapy during the course of their disease because of its superior efficacy over other antiparkinsonian therapies. However, long-term treatment with levodopa is often associated with the development of response fluctuations and dyskinesia, affecting up to 50% of patients within two years of therapy (Parkinson Study Group, 1996, 2000). While the mechanisms underlying levodopa-related complications are incompletely understood, the short half-life of levodopa has been identified as a major contributor to the development of the wearing-off phenomenon (Obeso, 2004; Olanow, 2004). Moreover, the short half-life of levodopa, with consequent pulsatile stimulation of striatal dopamine receptors, has been implicated in the pathogenesis of drug-induced dyskinesia (Obeso, 2000, 2004). Consequently, attempts have been made to extend levodopa's duration of action in order to treat motor complications.

Levodopa is routinely administered in one tablet with a dopa-decarboxylase (DDC) inhibitor, such as carbidopa or benserazide, to reduce its peripheral metabolism and increase its elimination half-life, thereby minimizing the peripheral side-effects that are common when levodopa is given alone. With a catechol-O-methyl-transferase (COMT) inhibitor such as entacapone, the elimination half-life of levodopa can be further increased (Myllyla, 1993; Kaakkola, 1994; Merello, 1994; Nutt, 1994; Ruottinen, 1996). Entacapone has similar T_{max} and half-life values as levodopa (1 to 2 hours and 0.4 to 0.9 hours, respectively) and accordingly is routinely administered in combination with each dose of levodopa to enhance the bioavailability of levodopa (Gordin, 2003). The enhanced levodopa bioavailability that is achieved by including entacapone in the levodopa regimen has been proven in a number of Phase III studies to reduce 'off' time and increase 'on' time in PD patients with motor fluctuations (Parkinson Study Group 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Larsen, 2003). Carbidopa, levodopa and entacapone have now been combined in a single tablet with the brand name, Stalevo. At present, the safety of this drug is based on its bioequivalence to carbidopa/levodopa plus entacapone in healthy subjects (Heikkinen, 2002). Although previous studies in patients with PD have established the safety and tolerability profile of

carbidopa/levodopa and entacapone taken separately, there are no studies with this new levodopa formulation. Such practical information is vital when making the decision to modify or alter a patients' current therapy and it is important to rule out any unforeseen issues that may arise when combining the three components. The main indication for Stalevo is to replace immediate-release carbidopa/levodopa in patients experiencing wearing-off. Therefore, the primary aim of the present study was to assess the safety and tolerability of a direct switch from immediate-release carbidopa/levodopa to Stalevo in PD patients experiencing wearing-off.

Methods

Study design

A multicenter, open-label, single-arm 4-week investigation of Stalevo was performed. All subjects who completed the 4-week study were eligible to enter a 3-month open-label extension phase. The study was conducted at 23 centers in the United States and approved by the Institutional Review Board (IRB) at each study site. The data reported in this paper includes the 4-week data.

Subjects

Male and female subjects aged 30 years or older, with a clinical diagnosis of idiopathic PD exhibiting at least two out of three symptoms (rigidity, resting tremor, bradykinesia) and experiencing wearing-off, with or without mild dyskinesia, as determined by the study investigator, were enrolled in the study. Wearing-off was defined as the daily recurrence of PD symptoms at the end of at least one dose of levodopa during waking hours. Patients 'with dyskinesia' were defined as having a history of non-disabling involuntary movements associated with one or more doses of levodopa daily. These subjects scored '1' on the Unified Parkinson's Disease Rating Scale (UPDRS) question 32 ('What proportion of the waking day are dyskinesia present?'), and '0' or '1' on UPDRS question 33 ('How disabling are the dyskinesia?'). 'Without dyskinesia' was defined as a history of no dyskinesia, or mild dyskinesia not occurring on a daily basis. These subjects scored '0' on UPDRS question 32, and a '0' on question 33.

All subjects were receiving a stable dose of immediate-release formulation carbidopa/levodopa 25/100 (1/2, 1 or 1½ tablets) for at least 1 month prior to study entry. Other antiparkinsonian medications such as dopamine agonists and selegiline (at a dose not exceeding 10 mg/day) were permitted, provided subjects were on stable doses for at least 1 month prior to study entry and that the dose remained unchanged throughout the study.

Exclusion criteria included: previous or current use of entacapone or tolcapone; a history, signs or symptoms suggestive of secondary or atypical parkinsonism; unstable PD requiring booster doses or prn dose regimens of levodopa; presence of disabling dyskinesia (a score of $\geq$2 on UPDRS question 32, or a score of $\geq$2 on UPDRS question 33); use of controlled release or extended release carbidopa/levodopa, $<$3 or $>$5 times daily doses of immediate-release carbidopa/levodopa 25/100, or immediate-release carbidopa/levodopa 10/100 or 25/250; concomitant use of monoamine oxidase (MAO)-B inhibitors (except selegiline) or neuroleptics within 60 days prior to study entry; previous history of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis.

Study treatment and protocol

At study entry, subjects were directly switched from immediate-release carbidopa/levodopa to Stalevo so that the carbidopa/levodopa dose was equivalent (e.g. Stalevo 50 [12.5/50/200], Stalevo 100 [25/100/200] or Stalevo 150 [37.5/150/200]) and doses were administered at the same time of day as the pre-study medication. Dose reductions were permitted if deemed

clinically necessary by the study investigator during follow-up. Assessments were made by the same investigator throughout the study. Patients visited the clinic at Day 0 and on their final visit (Day 28 or early termination), and were followed up by telephone at Days 2, 7, and 14. Compliance was assessed by the residual number of entacapone tablets (expected versus residual tablets) at the final study visit.

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. All patients provided written informed consent.

Tolerability and safety evaluations

Intolerability of Stalevo was defined as the percentage of subjects who discontinued the study due to side effects (early termination). This was the primary outcome of the study. Secondary tolerability variables included: percentage of subjects experiencing new onset dyskinesia, and percentage of subjects experiencing worsening of pre-existing dyskinesia. Safety evaluations consisted of monitoring and recording all adverse events (at each study visit) and measurement of vital signs, EKGs, physical examination and hematology, blood chemistry and urine values (at baseline and final visit).

Efficacy assessments

Efficacy was evaluated by change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) (part II, part III and parts II + III). 'Off' time was evaluated using the UPDRS question 39 (categorized as: none of the waking day; 1–25%, 26–50%, 51–75%, and 75–100% of the waking day). Quality of life was evaluated by the change from baseline in Parkinson's Disease Questionnaire-39 (PDQ-39) total score. Investigator and patient global clinical assessments and change in the total levodopa dose were also assessed.

Statistical methods

The level of significance was set at 0.05. An intent-to-treat population, consisting of all subjects who received study medication and who had at least one post-baseline efficacy assessment, was used for the efficacy evaluation. A safety population, consisting of all subjects who received at least one dose of study medication, was used for the safety and tolerability analyses. Continuous variables were summarized by sample size, mean, and standard deviation. Discrete variables were summarized by frequencies and percentages. Changes from baseline were analyzed using paired t-tests, except change from baseline in UPDRS question 39 where a Wilcoxon Signed Rank test was used.

Results

Subjects

The baseline clinical characteristics are summarized in Table 1. Subjects had mild disease, as indicated by UPDRS II and III scores. Thirty-nine of 169 subjects (23.1%) had mild dyskinesia at study entry.

The majority of subjects (125/169 [74.0%]) received concomitant antiparkinsonian medication with 103/169 (61.0%) of patients receiving a dopamine agonist. Other antiparkinsonian medications included MAO-B inhibitors (22/169 [13.0%]) subjects and amantadine (15/169 subjects [9.0%]).

Tolerability and safety

Eight percent (14/169) of patients discontinued the study. One patient withdrew consent and another withdrew due to a lack of efficacy. Seven percent (12/169) discontinued due to an adverse drug reaction, including nausea, continued or

Table 1. Baseline patient characteristics

Characteristic	Patients (n = 169)
Sex, n (%)	
Male	111 (65.7%)
Female	58 (34.3%)
Age, yrs (mean ± SD)	65.9 ± 11.2
Duration of PD, yrs (mean ± SD)	5.23 ± 3.7
Hoehn-Yahr stage (mean ± SD)	2.28 ± 0.60
Total daily levodopa dose, mg/day (mean ± SD)	4.27 ± 133.9
Dyskinesia, n (%)	39 (23.1%)
Concomitant medications, n (%)	
Dopamine agonists	103 (60.9%)
Pramipexole	51 (30.2%)
Ropinirole	54 (32.0%)
Pergolide	19 (11.2%)
Selegiline	22 (13.0%)
Amantadine	15 (8.9%)

SD standard deviation

worsening of 'off' periods, blurred vision, lightheadedness, headache, deterioration of motor function, vivid dreams, agitation, pressure on chest, joint pain and increased rigidity.

Eleven of the 130 subjects (8.5%) who did not have dyskinesia at study entry developed dyskinesia and 17/39 subjects (43.6%) with pre-existing dyskinesia experienced worsening of their dyskinesia. The majority of subjects who either developed new onset dyskinesia or had worsening of pre-existing dyskinesia, experienced an improvement in their dyskinesia with a reduction in Stalevo dose or returned to baseline levels without a dose change. Overall, the mean daily dose of levodopa was maintained from baseline to final visit

Table 2. Adverse reactions during treatment

Adverse event	Number of patients, n (%)
Nausea	21 (12.4%)
Dizziness	11 (6.5%)
Somnolence	11 (6.5%)
Chromaturia	11 (6.5%)
Constipation	8 (4.7%)
Headache	7 (4.1%)
Tremor	7 (4.1%)
Diarrhea	5 (3.0%)
Abnormal dreams	5 (3.0%)
Asthenia	5 (3.0%)
Insomnia	5 (3.0%)
Anxiety	4 (2.4%)
Fatigue	4 (2.4%)
Back pain	4 (2.4%)
Pain in extremity	4 (2.4%)

Table 3. Effect of Stalevo on efficacy

Scale	Baseline	Endpoint	Reduction from baseline	p-value
UPDRS				
Part II	11.0 ± 6.0	9.3 ± 5.4	1.7 ± 3.8	<0.001
Part III	24.4 ± 12.5	20.4 ± 11.2	3.9 ± 8.0	<0.001
Parts II + III	35.4 ± 16.8	29.8 ± 15.0	5.6 ± 10.4	<0.001
Question 39	1.3 ± 0.6	1.1 ± 0.6	0.3 ± 0.8	<0.001
PDQ-39				
Total score	35.7 ± 15.2	31.8 ± 13.4	4.0 ± 9.9	<0.001

Mean values plus or minus standard deviations are shown

(404.1 ± 134.7 mg/day; 406.8 ± 144.0 mg/day, respectively). Similarly, the overall daily levodopa dose for patients with (438.5 ± 155.8 mg/day; 428.2 ± 173.5 mg/day, respectively) and without (393.8 ± 126.5 mg/day; 400.4 ± 134.0 mg/day, respectively) dyskinesia remained stable throughout the study period. All adverse events were rated as mild and were infrequent (Table 2). Nausea, dizziness, somnolence and chromaturia were the most frequently reported adverse events. No clinically relevant findings were recorded for vital signs or laboratory tests and there were no significant changes in liver enzyme function.

Efficacy

UPDRS scores (parts II, III, II + III, and question 39) and PDQ-39 were statistically significantly improved from baseline to study endpoint with Stalevo treatment (Table 3). Assessment of quartile shifts to evaluate change in 'off'

Table 4. Investigator and patient assessment of change in PD at endpoint compared with baseline

	Number of subjects, n (%)
Investigators' assessment	
Very much improved	5 (3.0)
Much improved	39 (23.1)
Slightly improved	71 (42.0)
No change	32 (18.9)
Slightly deteriorated	19 (11.2)
Much deteriorated	0 (0)
Very much deteriorated	1 (0.6)
Patients' assessment	
Very much improved	10 (5.9)
Much improved	47 (27.8)
Slightly improved	59 (34.9)
No change	28 (16.6)
Slightly deteriorated	19 (11.2)
Much deteriorated	4 (2.4)
Very much deteriorated	0 (0)

time showed that 53/167 subjects (31.7%) decreased at least one quartile of 'off' time during the waking day ($p < 0.001$), 102/167 subjects (61.1%) had no change and only 12/167 (7.2%) had worsening.

Both investigators and patients noted global improvement on treatment. At endpoint, investigators reported some degree of improvement in 115/169 subjects (68.1%), and 116/169 patients (68.6%) reported improvements (Table 4).

Discussion

In this first study to evaluate the safety and tolerability of Stalevo, it was found to be well tolerated in PD patients experiencing wearing-off. Only 7% of the subjects discontinued therapy due to side effects and adverse events were mild and uncommon. The 4-week duration of this study should have been of sufficient time to evaluate tolerability and discontinuation rates, since the majority of discontinuations during the pivotal entacapone clinical studies occurred within the first few weeks of treatment initiation (Parkinson Study Group, 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Larsen, 2003). The favorable tolerability and safety profile reported here is comparable to that reported in entacapone clinical trials in levodopa-treated PD patients with or without wearing-off (Parkinson Study Group, 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Hubble, 2003; Larsen, 2003).

The increase in dyskinesia following the switch to Stalevo treatment was not unexpected, as it occurred in previous studies with entacapone. The increase in dyskinesia is a result of enhanced dopaminergic activity (Parkinson Study Group, 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Larsen, 2003). Dyskinesia was often ameliorated with Stalevo dose reduction. Lowering the daily dose of levodopa has been successful in managing dyskinesia in entacapone clinical trials, where dose reductions were reported in subjects with more advanced disease (Parkinson Study Group, 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Larsen, 2003).

Efficacy assessments must be cautiously interpreted because of the open-label design used. However, the improvement in the UPDRS subscales, quality of life measure, and global clinical assessments reported are consistent with the results of blinded, controlled entacapone studies. The quality of life measure used, the PDQ-39, is a PD-specific instrument that is sensitive to changes to aspects of a patient's life other than those identified by clinical ratings (Wheatley, 2002). Improvement of patient quality of life with co-administration of entacapone with carbidopa/levodopa therapy has been previously reported (Durif, 2001; Gershanik, 2003). Also, the addition of entacapone has consistently resulted in improvement of the UPDRS III score from baseline in studies of both non-fluctuating and fluctuating levodopa-treated patients (Parkinson Study Group, 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Larsen, 2003). Stalevo treatment resulted in a decrease in 'off' time as assessed by UPDRS question 39. This improvement in 'off' time is consistent with previous entacapone studies which demonstrated an increase in mean daily 'on' time and a corresponding decrease in 'off' time (Parkinson Study Group, 1997; Rinne, 1998; Myllyla, 2001; Poewe, 2002; Brooks, 2003; Larsen, 2003).

Although the present study was open-label, it did include relatively strict exclusion criteria; patients receiving 5 or more doses of carbidopa/levodopa 25/100 and/or experiencing moderate or severe dyskinesia were not eligible for the study. These criteria were implemented in line with regulatory recommendations as clinical studies with levodopa and entacapone have shown that patients experiencing moderate or severe dyskinesia and/or receiving higher daily levodopa doses at baseline are likely to require a reduction in daily levodopa dose when entacapone is added to their treatment. It will therefore be of interest to evaluate the tolerability and efficacy of Stalevo in a wider patient population including patients with more advanced disease.

Current knowledge regarding the potential mechanisms underlying the development of motor complications increased. It may therefore be possible to optimize levodopa treatment to reduce the risk of inducing motor complications (Olanow, 2004). Accumulating evidence suggests that therapies which are less likely to induce pulsatile stimulation and provide more continuous dopaminergic stimulation are associated with a reduced propensity to induce motor complications (Obeso, 2004; Stocchi, 2004). In this regard, the short half-life of traditional levodopa formulations makes it less than ideal. It is now established that combining entacapone with levodopa enhances the pharmacokinetic profile of levodopa in patients experiencing motor complications. The critical question is whether delivery of levodopa with entacapone will extend the plasma half life sufficiently to avoid pulsatile stimulation of striatal dopamine receptors and so avoid the development of complications. The frequent administration of levodopa and entacapone may provide stable plasma levels (Stocchi, 2004). However, the optimal dose and timing (‘‘dose interval’’ instead of ‘‘timing’’?) of Stalevo that will consistently provide suitably stable plasma levels remains to be determined. A long-term clinical trial in early PD patients is clearly needed to evaluate the potential of Stalevo in early PD patients.

In conclusion, this is the first study to demonstrate that Stalevo is well tolerated and safe for the treatment of PD patients with wearing-off. Moreover, Stalevo appears to provide the clinical improvements previously established with separate carbidopa/levodopa and entacapone.

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Appendix

The principle investigators (and study co-ordinators) of the SELECT-TC trial are as follows:

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