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Efficacy and Tolerability of Entacapone Versus Cabergoline in Parkinsonian Patients Suffering from Wearing-Off

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Abstract: In this 12-wk, multi-center, randomized, open-label, rater-blinded study, efficacy and tolerability of Entacapone (ENT) or Cabergoline (CBG) in conjunction with levodopa were compared in 161 older Parkinson's disease patients with wearing-off. Patients received either ENT, 3 to 5 times daily, or CBG, titrated according to requirements to a maximum of 6 mg/d. A significant decrease of nearly 2 hours in the daily OFF-time (primary efficacy variable) was recorded in both treatment groups. The non-inferiority test failed despite a trend in favor of ENT. Reduction in OFF-time occurred faster in the ENT compared to the CBG treated patients. A decrease of ~20% was detected in parts II and III of the UPDRS, with no differences between the groups. Forty-three percent of the patients in the ENT group reported dyskinesias at baseline, and 35% at the final visit. The corresponding figures in the CBG group were 46% and 43%. Quality of life, measured by PDQ-39, increased substantially with both ENT and CBG. The mean daily dosage at the final visit was 698 mg for ENT (plus 447 mg levodopa) and 3.45 mg for CBG (plus 475 mg levodopa). Adverse events (AE), leading to discontinuation, were reported in 8.5% of the ENT and 13.9% of the CBG treated patients. Nausea was the most common AE in each group, corresponding figures being 7.3% with ENT and 25.3% with CBG ($P = 0.0024$). A probable or possible causal relationship with ENT was reported in 41% and with CBG in 64% of the AE. Among these, only one serious AE (dehydration) was recorded with each treatment group. ENT and CBG reduced the patient's motor complications effectively and to a similar degree. The clinical benefit was more quickly apparent with ENT, which also showed a more favorable AE profile than CBG. © 2007 Movement Disorder Society

Key words: COMT inhibition; Entacapone; Cabergoline; Parkinson's disease; clinical trial; wearing-off

One of the main problems in the treatment of Parkinson's disease (PD) is the emergence of motor fluctuations and dyskinesias, which occur with an annual incidence of about 10%.[1] Recent studies recorded an even higher incidence of wearing-off within 1 to 2 yr.[2,3] Evidence suggests that progressive loss of nigro-striatal dopaminergic neurons and the subsequently reduced dopamine storage capacity are key factors for these complications.

The preferred therapeutic strategies are either to add a dopamine agonist or a COMT-inhibitor to levodopa[4,5] as both provide a more continuous dopamine receptor stimulation and have been shown to prevent and improve motor fluctuations in the case of dopamine agonists,[6,7] and to improve fluctuations in the case of COMT-inhibitors.[8,9] Many dopamine agonists are available, one of which being Cabergoline (CBG), a potent ergot struc-

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tured agonist with a longer elimination half-life when compared to other dopamine agonists.[10] Two COMT inhibitors are available.[11,12] The first of these being Entacapone (ENT), a peripherally acting COMT-inhibitor, which extends the elimination half-life of L-dopa, increases its bioavailability, and minimizes the variability in L-dopa plasma levels. The other Tolcapone requires special monitoring due to potential liver toxicity and is therefore only recommended as a second line drug.[13]

Guidelines[4,5] for the treatment of older patients recommend commencing with L-dopa, with the subsequent addition of either a dopamine agonist or ENT. Although 2 studies are available comparing Tolcapone with Pergolide or Bromocriptine,[9,12] a similar comparison of ENT with a dopamine agonist has never been published. The aim of the present study was thus to compare the efficacy and tolerability of ENT and CBG as adjuncts to L-dopa in the treatment of older PD patients with wearing-off.

PATIENTS AND METHODS

The study has been carried out as a multi-center, randomized, parallel-group trial comparing ENT (Orion Pharma, Espoo, Finland) with CBG (Pharmacia, Erlangen, Germany) as adjuncts to L-dopa/Carbidopa or L-dopa/Benserazide. An open design for 12 wk was chosen due to different dosing schemes for the study drugs. Patients examinations were performed by the hospital or practice physician and evaluation of the Unified Parkinson's Disease Rating Scale (UPDRS)[14] and the Dyskinesia-Score[15] was carried out by blinded raters, who were experts in movement disorders. Care was taken to ensure that the same rater was used at both baseline and final visits. The study was conducted in 27 centers in Germany and in 3 centers in Lithuania. The Ethics Committee of the Medical faculty of the Christian-Albrechts-University in Kiel and the Bioethics Committee of Lithuania approved the protocol prior to commencing the study. The patients were given both oral and written information concerning the study, and signed a written consent form prior to participation.

All eligible patients were assigned randomly to one of the two treatment regimens: ENT 200 mg concomitantly with each of the 3 to 5 daily doses of L-dopa or CBG taken once daily. CBG was individually titrated with an initial dosage of 1 mg, rising according to requirements to a maximum of 6 mg/d over a period of 6 to 8 wk. The daily dosage of L-dopa could be reduced if necessary. The daily dosage of the study medication was kept constant for the last 4 wk prior to final assessment. In case of the occurrence of psychiatric complications (e.g. hallucinations) which made drug intervention with neuroleptics necessary, neuroleptic treatment was allowed with Clozapine only. With the occurrence of nausea and vomiting, the antiemetic Domperidone was permitted where treatment was found to be necessary.

PATIENTS

Inclusion Criteria

Male or female patients $\geq$60 yr with idiopathic PD and wearing-off, 3 to 5 daily doses of L-dopa; at least 60 min of daily OFF-time after the first ON-period in the morning; other anti-parkinsonian treatment had to be stable for 3 wk prior to randomization.

Exclusion Criteria

Mini-Mental-Status $\leq$26, Beck-Depression-Scale $\geq$17. Concomitant diseases precluding the proper study conduction. Treatment with non-selective MAO inhibitors. Treatment with drugs partly metabolized by the COMT enzyme. Use of Selegiline was allowed, with a maximal daily dosage of 10 mg. Patients were also excluded if they had already used a COMT inhibitor (ENT or Tolcapone) or a dopamine agonist within 4 wk prior to the randomization, or had a history of hypersensitivity to ergot derivates and ENT.

ASSESSMENTS

During the screening visit of 1 to 14 days prior to randomization the patients medical records were taken, vital signs measured, a physical examination performed, and safety laboratory tests analyzed. The Mini-Mental-Status and the Beck-Depression-Scale was also evaluated. The patients were trained in use of home diaries.

During visit 1 (baseline) the examination was performed and the inclusion and exclusion criteria were controlled. The UPDRS parts I to VI and the Dyskinesia-Score were performed by the blinded rater. The patients completed the Clinical Global Evaluation Scale (CGE), returned their home diaries and the PDQ 39.[16,17] The anti-parkinsonian and concomitant medication used was recorded, as well as adverse events (AE). The study medication was handed out to the patients according to the randomization code. Visits for dosage adaptation of L-dopa and study medication collecting the completed diaries and AE records were performed at weeks 2 (visit 2), 4 (visit 3), 6 (visit 4), and 12 (final visit, visit 5). Patients could contact their physician by phone if necessary. A comprehensive UPDRS evaluation, dyskinesia scoring, completing of PDQ-39 and CGE as well as a physical examination was repeated at the final visit. The results from the final visit were compared to baseline. Treatment compliance was evaluated by tablet counts.

FIG. 1. Study flow diagram.

Home Diaries

A home diary was handed out to the patients at the visits. The patients were advised to fill out the diary on the three consecutive days before the next examination visit. The diary covered 18 h per day, divided into 30 min intervals. For each time interval the patients were requested to report whether they were mobile (ON), ON with dyskinesias, immobile (OFF), or asleep. Both mean and standard deviation (SD) of the days recorded were calculated. The patients also recorded time and dosage of the L-dopa and study medication intake.

PDQ-39

The disease specific questionnaire PDQ-39 reflecting the patient's quality of life was completed by the patient at visit 1 and at the final visit. The PDQ-39 consists of 39 questions divided into 8 subscales (mobility, activities of daily living, emotional well being, stigma, social support, cognition, communication and bodily discomfort). The statistical analysis was based on the summary index score.

STATISTICS

The primary objective of this study was to prove non-inferiority of ENT compared to CBG, when used as adjuncts to L-dopa therapy, with the primary efficacy variable being changes from baseline in the total daily OFF-time after the first daily ON-time. A difference of 30 min OFF-time was predefined as the limit of non-relevant difference between the two treatments (non-inferiority margin). Primary analysis was carried out for the per-protocol (PP) data set by means of an ANCOVA model using the baseline value as a covariate.

Secondary efficacy variables, including the changes from baseline of total daily ON-time, PDQ-39, and UPDRS parts I-III, were tested on an exploratory basis for the intention-to-treat data set. The last observation carried forward method was applied using ANCOVA models (ITT-LOCF). Two-sided 95% confidence intervals for the differences in adjusted means were also calculated. Qualitative secondary efficacy variables were tested by applying the Fisher's exact test.

Sample size estimation was based on results from earlier controlled phase III studies.[8,18] The estimated standard deviation for the primary efficacy variable was 1.5 h. Application of the *t*-test model with $\alpha = 0.05$, $\beta = 0.20$, and a non-inferiority margin of 30 min resulted in a sample size of 112 evaluable patients per group.

RESULTS

A total of 187 patients were screened for the study. One hundred sixty-one patients were randomized, with 82 in the ENT group and 79 in the CBG group. Of the randomized patients, 26 discontinued the study prematurely, 13 in each treatment group (Fig. 1). Patient characteristics and PD history are shown in Table 1.

In the ENT group 20 patients were taking Amantadine and 7 Selegiline, and in the CBG group 29 patients were taking Amantadine and 7 Selegiline.

Efficacy

The daily OFF-time after the first daily ON-period was significantly reduced from baseline with ENT by 1.9 h and with CBG by 1.6 h. PP and ITT-LOCF analyses showed similar results (Table 2). With ENT was a clear

TABLE 1. *Baseline patient characteristics*

	Entacapone	Cabergoline
Patients (n)	82	79
Male/Female (n)	48/34	51/28
Age (years)	69.9 ± 7.4	70.3 ± 6.4
Time since first diagnosis of PD (years)	5.7 ± 4.6	5.5 ± 4.3
Duration of fluctuations (years)	1.7 ± 2.3	1.6 ± 2.0
Duration of Levodopa therapy (years)	4.9 ± 4.3	4.4 ± 4.2
Total daily Levodopa dosage (mg)	467 ± 281	497 ± 273
Hoehn & Yahr stage 2 to 3 (n)	58	66
Other anti-parkinsonian medication		
Selegiline (n (%))	7 (8.5)	7 (8.9)
Amantadine (n (%))	20 (24.4)	29 (36.7)
Others (n (%))	5 (6.1)	3 (3.8)

Values are mean ± SD when appropriate.

TABLE 2. *Efficacy variables in the Entacapone and Cabergoline treated patients*

Efficacy variables	Entacapone				Cabergoline				CI_{95}	*P*
	n	Baseline	Final visit	Difference	n	Baseline	Final visit	Difference		
Daily OFF-time after first ON-period (h) (primary efficacy variable)[a]	65	4.0 ± 2.0	2.1 ± 2.3	−1.9 ± 2.7	59	3.8 ± 2.5	2.2 ± 2.2	−1.6 ± 2.3	−0.89; 0.63	0.742
Daily OFF-time after first ON-period (h) (primary efficacy variable)	71	3.8 ± 2.1	2.0 ± 2.3	−1.8 ± 2.7	64	3.7 ± 2.6	2.0 ± 2.2	−1.7 ± 2.4	−0.78; 0.65	0.857
Total daily ON-time (h)	72	8.1 ± 2.7	10.3 ± 3.2	2.2 ± 3.4	65	8.3 ± 3.3	10.6 ± 2.9	2.3 ± 2.8	−1.14; 0.69	0.627
Proportion of daily ON-time (%)	72	61 ± 19	77 ± 22	16 ± 25	65	61 ± 23	77 ± 20	16 ± 19	−6.6; 6.3	0.971
ON-time with dyskinesia (h)	72	0.5 ± 1.1	0.4 ± 1.0	−0.1 ± 1.2	65	0.4 ± 0.8	0.5 ± 1.2	0.1 ± 1.1	−0.48; 0.21	0.449
UPDRS, Part I	69	2.0 ± 2.1	1.8 ± 2.0	−0.2 ± 1.5	69	1.5 ± 1.9	1.3 ± 1.9	−0.2 ± 1.1	−0.30; 0.51	0.615
UPDRS, Part II	69	13.4 ± 6.7	10.9 ± 5.7	−2.5 ± 3.5	69	13.0 ± 5.9	10.5 ± 5.1	−2.5 ± 3.9	−0.91; 1.23	0.765
UPDRS, Part III	69	32.2 ± 16.5	26.0 ± 13.5	−6.3 ± 8.7	69	29.6 ± 14.5	23.3 ± 11.3	−6.3 ± 7.9	−1.37; 3.12	0.441
PDQ-39, summary index	66	28.3 ± 14.7	24.9 ± 14.8	−3.4 ± 10.3	65	28.0 ± 12.7	21.7 ± 12.8	−6.3 ± 10.0	−0.32; 6.26	0.076
Levodopa dose (mg)	77	479 ± 286	447 ± 253	−32 ± 128	71	486 ± 270	475 ± 260	−11 ± 63	−53.7; 12.6	0.211

[a] Per-protocol analyses (PP); All other efficacy analyses are intention-to-treat last observation carried forward (ITT-LOCF). Confidence intervals and *P*-values refer to treatment differences (ENT minus CBG) in changes from baseline.

reduction in OFF-time already seen at 2 wk (Fig. 2). Although the results for the primary efficacy variable were similar, non-inferiority could not be proven as the upper limit of the confidence interval used for the test was 30.5 min, which therefore just failed to be below the predefined non-inferiority margin of 30 min. This was mainly due to the fact that the achieved sample size was too small.

Both drugs caused similar reductions in the UPDRS II and III subscales of ~20%. Forty-three percent of the patients in the ENT group reported dyskinesias at baseline, 35% at the final visit. The corresponding figures in the CBG group were 46% and 43%. There was also a decrease in dyskinesias according to the Dyskinesia-Score from 26.1% to 20.3% in the ENT group and from 19.1% to 13.2% in the CBG group (all patients with a score >1 were included). The patients had a reduction of their Hoehn and Yahr stage in 44% of the ENT and in 39% of the CBG group. The Schwab and England score improved for 56% of the patients in the ENT and for 46% in the CBG group. The mean daily dosage at the final visit was 698 mg for ENT (plus 447 mg L-dopa) and 3.45 mg for CBG (plus 475 mg L-dopa). The summary index score of the PDQ-39 at baseline was 28% for both ENT and CBG, and both groups showed a significant decrease. The CGE scores were also strongly improved. No significant differences were found between the treatment groups in any of the secondary efficacy parameters when comparing results of the final visit to baseline. The detailed efficacy variables in the ENT and the CBG group are presented in Table 2.

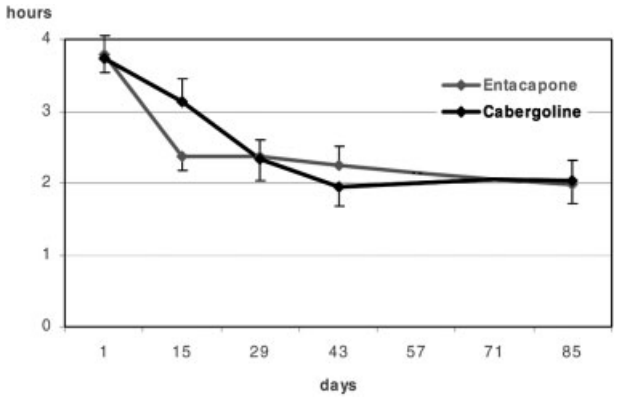

FIG. 2. Daily OFF-time after first ON-period* (h) (mean ± SEM). *ITT population.

Safety

Overall 44 patients (53.7%) treated with ENT and 42 patients (53.2%) treated with CBG reported AE. These were serious (SAE) in 6 patients (7.3%) in the ENT group and in 3 patients (3.8%) in the CBG group. However, the only SAE with a probable or possible causal relationship to the study medication was dehydration, reported in 1 ENT patient due to diarrhea and in 1 CBG patient with unknown cause. In the CBG group, 11 patients (13.9%) discontinued the study due to AE, the corresponding figures being 7 (8.5%) in the ENT group. The AE reported by at least 3 patients in either group are summarized in Table 3.

Nausea was the most common AE with a significantly different occurrence between the groups, (25.3% CBG and 7.3% ENT, $P = 0.0024$). Diarrhea was the most frequent non-dopaminergic AE, occurring in 7.3% of the patients on ENT and 3.8% on CBG. A probable or possible causal relationship with ENT was judged in 41% and with CBG in 64% of the AE by the investiga-

TABLE 3. *Incidence rates of the most frequently reported AE*

	Patients (%)		
	Entacapone (n = 82)	Cabergoline (n = 79)	Significance P
Nausea	7.3	25.3	0.0024
Diarrhea	7.3	3.8	
Fatigue	7.3	3.8	
Dizziness	4.9	5.1	
Vertigo	2.4	7.6	
Headache	3.7	5.1	
Somnolence	2.4	6.3	
Constipation	2.4	5.1	
Chromaturia	6.1	0.0	
Hallucinations	3.7	3.8	
Sleep Disorders	2.4	3.8	
Tremor	3.7	2.5	
Dry mouth	1.2	3.8	
Fall	1.2	3.8	
Oedema, peripheral	1.2	3.8	
Orthostatic hypotension	3.7	0.0	

Preferred terms coded according to MedDRA dictionary. ≥3 patients in either group.

tors (Table 4). According to this classification nausea was still more common in the CBG group, Chromaturia was only seen in the ENT group. Somnolence, dizziness, and in particular vertigo were clearly more common in the CBG group. No significant changes occurred in any of the safety laboratory values or vital signs in either group.

DISCUSSION

This study has compared ENT and CBG in patients with fluctuating PD. In both groups the daily OFF-time was reduced by about 45% in the PP and ITT-LOCF data set. Accordingly the daily ON-time of ~8 h at baseline was increased by more than 2 h. These results were consistent with previous controlled studies with ENT and CBG, whereby a reduced OFF-time of about 1 to 2 h was found.[8,18-20]

Nevertheless, this study failed to demonstrate non-inferiority for ENT. The calculated sample size of 224 patients for PP data set was not reached for practical reasons such as problems in recruitment. The upper limit of the confidence interval used for the non-inferiority test was 30.5 min and thus just failed to be below the predefined non-inferiority margin of 30 min.

Two earlier studies have compared the COMT inhibitor Tolcapone with a dopamine agonist in PD patients with motor fluctuations. In these studies, Bromocriptine[12] and Pergolide[9] decreased OFF-time and increased ON-time to a similar degree of ~2 h as seen in our study. In all the studies comparing a COMT inhibitor with a dopamine agonist a double-blind design was not employed because of the different dosing schemes for these 2 types of compounds. CBG, as with other dopamine agonists, has to be titrated slowly, and thus its maximum effect is only seen after a few weeks. This phenomenon was also found in the present study. The full effect of ENT was already seen at the first visit after 2 wk while that of CBG occurred only later.

Quality of life was assessed using the PDQ-39, and both drugs significantly improved the score on this scale. This was even more pronounced for CBG although the difference was not significant. It has earlier been shown that already minimal changes in the PDQ-39 are clinically relevant.[21] Our results should therefore be meaningful for most patients. This is also confirmed by the improvement of the CGE scores.

To get a better impression of the tolerability profile of a drug, it seems to be more appropriate to refer to AE with a potential positive causal relationship according to assessment of the investigators. Nausea was the most common dopaminergic AE reported in 21.5% of the patients in the CBG group, while much less common in the ENT group (3.7%). Vertigo and disturbances such as dizziness and somnolence were also reported more frequently in the CBG than in the ENT group.

In contrast to previous studies, orthostatic hypotension was not found in the CBG treated patients.[10] Compared with other studies the occurrence of the AE hallucination was extremely rare, despite the relatively old age of the study population.[10] This may well be due to the necessary slow titration scheme of CBG and the rigid exclusion of patients with dementia and depression.

One of the most frequent non-dopaminergic AE with both ENT and CBG was diarrhea. As in previous studies, very few laboratory safety test abnormalities were reported in this study. Not one case of elevated transaminase values was found in the ENT treated patients. This is in accordance with the results of larger long-term

TABLE 4. *AE with a probable/possible causal relationship*

	Patients (%)	
	Entacapone (n = 82)	Cabergoline (n = 79)
Nausea	3.7	21.5
Diarrhoea	3.7	3.8
Fatigue	3.7	3.8
Somnolence	2.4	5.1
Dizziness	1.2	5.1
Headache	2.4	3.8
Vertigo	0.0	6.3
Chromaturia	4.9	0.0
Dry mouth	1.2	3.8

Preferred terms coded according to MedDRA dictionary. ≥3 patients in either group.

clinical studies, as well as from general clinical practice, once again confirming that ENT is not associated with liver toxicity[18,19].

A separate analysis of patients ≥70 years confirmed in general the previous results; however, the difference in OFF-time reduction was more extensive (1.6 h ENT vs 1.2 h CBG, ITT-LOCF) and hallucinations occurred slightly more frequently in the CBG group.

In conclusion, both ENT and CBG used in conjunction with L-dopa in PD patients with wearing-off phenomenon were effective in reducing OFF-time, increasing ON-time and improving the patients' motor complications. Other efficacy parameters were also improved by both drugs, and again to a similar degree. The clinical benefit of ENT was recorded earlier than for CBG.

Both drugs also improved the quality of life in PD patients, while ENT was better tolerated, since it caused significantly fewer AE with a positive causal relationship.

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