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No correlation between COMT genotype and entacapone benefits in Parkinson's disease

[1*]Ji Seon Kim *MD*, [2*]Ji-Young Kim *MD*, [4]Jong-Min Kim *MD PhD*, [5]Jae Woo Kim *MD*, [6]Sun Ju Chung *MD PhD*, [6]Sung R Kim *RN*, [6]Mi J. Kim *MD*, [7]Hee-Tae Kim *MD*, [8]Kyoung-Gyu Choi *MD*, [1]Dong-Ick Shin *MD*, [9]Young Hee Sung *MD*, [10]Kwang-Soo Lee *MD*, [3]Han-Joon Kim *MD*, [11]Jinwhan Cho *MD*, [12]Mee Young Park *MD*, [13]Hyun-Young Park *MD*, [14]Seong-Min Choi *MD*, [15]Kun-Woo Park *MD*, [16]Ho-Won Lee *MD*, [17]Tae-Beom Ahn *MD*, [18]Oh Dae Kwon *MD*, [19]Sang-Jin Kim *MD*, [3]Beom S Jeon *MD PhD*

[1]Department of Neurology, Chungbuk National University College of Medicine, [2]Inje University Seoul Paik Hospital, [3]Seoul National University College of Medicine, [4]Seoul National University College of Medicine Bundang Hospital, [5]Dong-A University College of Medicine, [6]University of Ulsan College of Medicine, [7]Hanyang University College of Medicine, [8]Ewha Womans University College of Medicine, [9]Gachon University College of Medicine, [10]Catholic University of Korea College of Medicine, [11]Samsung Medical Center Sungkyunkwan University School of Medicine, [12]Yeungnam University College of Medicine, [13]Wonkwang University School of Medicine, [14]Chonnam National University Medical School, [15]Korea University College of Medicine, [16]Brain Science and Engineering Institute, Kyungpook National University College of Medicine, [17]Kyung Hee University College of Medicine, [18]Catholic University of Daegu School of Medicine, [19]Inje University College of Medicine
*The authors contributed equally to this work.

Abstract

Catechol-*O*-methyltransferase (COMT) inhibitors are used to increase the bioavailability of therapeutic L-dopa. We examined the efficacy of entacapone in Parkinson's disease patients who had daily "off" duration of ≤2 hours, and carried different COMT polymorphisms. A total of 168 PD patients were recruited from 19 centers. Subjects were administered with 100–200 mg of entacapone in combination with each dose of L-dopa for 2 months. The clinical efficacy was evaluated based on the activities of daily living (ADL), score on the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr (H&Y) stage, and Clinical Global Impression (CGI). COMT polymorphisms were genotyped. 3-O-methyldopa (3-OMD) levels were measured before and after the administration of entacapone. Entacapone administration produced significant improvements in the total daily "on" duration, ADL, UPDRS score, and H&Y stage. Nineteen patients (11.3%) had the low-activity COMT genotype, 68 patients (40.5%) had the intermediate-activity COMT genotype, and 81patients (48.2%) had the high-activity COMT genotype. The efficacy, and adverse effects of entacapone therapy did not differ between the three groups. There was a significant reduction in 3-OMD, but this did not differ among the three genotypes. Entacapone provided an increased "on" duration and improved motor function in all COMT genotypes.

INTRODUCTION

L-dopa is the most effective treatment for Parkinson's disease (PD). However, side effects are associated with administered L-dopa being heavily decarboxylated into dopamine in the periphery. Therefore, peripherally acting dopa decarboxylase (DDC) inhibitors such as carbidopa or benserazide are combined with L-dopa to increase the bioavailability of L-dopa and reduce these side effects. When DDC inhibitors are used, 3-O-methylation of L-dopa becomes a significant shunting pathway leading to 3-O-methyldopa (3-OMD) and thus reducing the bioavailability of L-dopa.[1] Therefore, catechol-*O*-methyltransferase (COMT) inhibitors were developed to block the peripheral shunting of L-dopa and thereby increase the bioavailability and extend the half-life of L-dopa.[2]

Two COMT inhibitor compounds, tolcapone and entacapone, have been introduced into clinical

Address correspondence to: Beom S. Jeon, Department of Neurology, Seoul National University, Seoul, 110-744, Korea. Tel: +82-2-2072-2876, FAX: +82-2-3672-7553, e-mail: brain@snu.ac.kr

usage, but the liver toxicity of tolcapone has made entacapone the most widely administered. The benefits of combining L-dopa/DDC inhibitor with entacapone have been confirmed in several clinical studies, mainly in terms of reducing motor fluctuations.[3-7]

The COMT gene in humans is localized to chromosome 22, band q11.2 and is polymorphic with a trimodal distribution of low ($COMT^{AA}$), intermediate ($COMT^{GA}$), and high ($COMT^{GG}$) activities.[8] This polymorphism, which is due to the alteration of a single encoded amino acid, leads to three to four fold differences in COMT activity in erythrocytes and other human tissues.[9-11]

The COMT genotypes could be expected to affect the response to COMT inhibitors, with high-activity COMT genotypes showing greater responses. Several studies have found that genetic polymorphisms significant influence individual variations in the biotransformation of L-dopa.[12-14] However, the results of other clinical studies were not consistent with predictions that a high-activity allele will produce greater benefits or more adverse events from COMT inhibitors.[15-17]

There may be several reasons for this discrepancy between the prediction and the observed responses. First, those studies were conducted in patients with "wearing-off" periods longer than 2 hours.[15] Those patients were probably relatively advanced fluctuators with severe dyskinesias, which may have made drug adjustment difficult. Second, only low numbers of each genotype were included.

Therefore, the present study selected patients with wearing-off periods shorter than 2 hours, thereby hoping that they were in the earlier stage of parkinsonism than those in the previous studies[15,17,18] and thus reducing the difficulty of severe dyskinesia. We achieved a sample size of 168 by recruiting from 19 Korean centers. Since 3-OMD is a metabolite of L-dopa by COMT, and thus may reflect the degree of COMT activity, pre- and post-treatment plasma levels of 3-OMD were measured to examine the correlations among the genotype, 3-OMD level, and the degree of benefit of entacapone therapy.

METHODS

Patients

One hundred and sixty-eight patients with PD were recruited from the "Entacapone Study Group", which includes 19 movement disorder centers in Korea. Inclusion criteria were (1) of Korean ethnicity and aged between 30 and 85 years, (2) fulfilling the criteria of the UK Parkinson's Disease Society Brain Bank for PD, (3) presence of a "wearing-off" period shorter than 2 hours (excluding the early morning "off" period), and (4) regular usage of daily stable dose of L-dopa and other drugs (e.g., anticholinergics, MAO-B inhibitor, or amantadine) for more than 1 month. Exclusion criteria were (1) presence of dementia, psychosis, major depression, or other severe neurologic problem; (2) hypersensitivity to COMT inhibitors and a history of metallotoxemia; (3) presence of severe medical disease; or (4) being pregnant or breast-feeding. The IRB approved the study, and written consent was obtained from each participant.

Study design

Candidate patients were educated to record a diary for 2 days about whether they were "on", "on" with dyskinesia, "off", or "asleep" before each visit. The mean duration of the "off" state in the diary was used as the "off" duration. When patients satisfied the inclusion criteria, the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr (H&Y) stage, and Schwab and England activities of daily living (ADL) were scored, and venous blood samples were drawn for determining the COMT genotype and 3-OMD level. The patients then started taking 100–200 mg of entacapone with each dose of L-dopa. The entacapone dose could be adjusted during the first 4 weeks by the clinician; when dyskinesia became problematic, L-dopa was reduced. Patients were examined at 4 and 8 weeks after adding entacapone based on the ADL, UPDRS, H&Y stage, and Clinical Global Impression (CGI). All patients recorded a diary for 2 days before each visit, and the mean "off" duration was calculated. Repeat blood sampling to measure 3-OMD was performed at 8 weeks after taking entacapone. Patients who took at least 80 % of the scheduled medications were included in the evaluation.

COMT genotyping

Genomic DNA was extracted from venous blood samples (10 ml), and the G158A COMT polymorphism was analyzed by PCR and enzymatic digestion (NIaIII).[9] Participants were divided into the following three groups based on the activity of the COMT genetic polymorphism: low ($COMT^{AA}$), intermediate ($COMT^{GA}$), and high ($COMT^{GG}$). Investigators and patients were blind to genotype throughout the study.

Measurement of 3-OMD level

Aliquots (10 ml) of venous blood were collected in EDTA tubes. The plasma was obtained by rapid centrifugation and then immediately frozen at –80°C until analysis. In centers where immediate centrifugation was not available, the blood samples were transferred to the central laboratory at Seoul National University Hospital (SNUH) by courier, and then the plasma was separated. And delay in separating the plasma was recorded. 3-OMD was measured by high-pressure liquid chromatography with coulometric detection.[19]

Statistics

The obtained showed normal distributions, and hence mean ± standard deviation (SD) values were calculated. Data for before and after entacapone treatment were compared using Student's *t*-test for paired observations and the chi-squared test. Comparisons of the efficacy of entacapone between patients in the three genetic groups were analyzed using one-way analysis of variance. The chi-square test was used to compare proportions of patients with side effects. The minimum level of statistical significance was set at 0.05 or less.

RESULTS

A total of 168 patients who fulfilled the inclusion criteria were enrolled. All of them were native Koreans, and their age ranged from 38 to 83 years (62.20±9.21 years). The mean disease duration was 6.64 years, and the mean duration of L-dopa treatment was 4.98 years (Table 1). Eleven patients were excluded due to poor compliance (<80% of the scheduled medication), and seven dropped early out due to adverse effects. Thus, data from the remaining 150 patients were entered into the final analyses (Table 2).

Two months after the initiation of entacapone treatment, the 24-hour home diaries indicated that there was a significant increase in the total daily "on" duration with a corresponding decrease in the total daily "off" duration. There were also statistically significant improvements in both the ADL and UPDRS (Parts I, II, III, and IV) scores during "on" duration evaluations (p<0.0001 for both) (Table 2).

Nineteen patients (11.3%) had the low-activity homozygous COMT genotype (A/A), 68 patients (40.5%) had the intermediate-activity heterozygous COMT genotype (G/A), and 81 patients (48.2%) had the high-activity homozygous COMT

Table 1: Demographic data of the study population

Characteristic (*N*=168)	Value (mean±SD)
Age (years)	62.2±9.2
Duration of PD (years)	6.6±3.7
Duration of L-dopa treatment (years)	4.9±3.4
LEDD (mg/day)	682.2±277.9
UPDRS Part III score	17.9±10.2
H&Y state, "on"	2.0±0.86
H&Y state, "off"	2.4±0.7
ADL, "on" (%)	87.4±11.3
ADL, "off" (%)	76.0±13.8
CGI	3.4±0.8

SD, standard deviation; PD, Parkinson's disease; LEDD, L-dopa equivalent daily dose; H&Y, Hoehn and Yahr; ADL. Activities of daily living; CGI, Clinical Global Impression

Table 2: Mean changes in scores after treatment with entacapone

Parameter (*N*=150)	Baseline	2 months later	*p*
"On" duration (hours)	14.3±2.1	14.9±2.3	<0.0001***
"Off" duration (hours)	1.6±0.5	1.2±1.1	<0.0001***
Dyskinesia (hours)	0.4±1.2	0.7±1.8	0.032***
LEDD (mg/day)	677.9±270.4	678.3±287.6	0.964
UPDRS I, "on"	1.2±1.7	1.0±1.6	0.137
UPDRS II, "on"	4.7±4.5	4.1±4.2	0.025***
UPDRS Part III, "on"	18.1±10.2	16.2±10.6	<0.0001***
UPDRS Part IV	4.2±2.4	4.1±2.8	0.492
H&Y state, "on"	2.0±0.8	2.0±0.8	0.711
† H&Y state, "off"	2.43±0.68	2.35±0.68	0.0009***
ADL, "on" (%)	87.3±11.5	89.1±11	<0.0001***
ADL, "off" (%)	75.6±14.0	78.6±12.8	<0.0001***

Values are expressed as mean ± standard deviation. *** indicated significant difference with $p<0.05$. The LEDD values shown here did not include entacapone. † This value presented to the second decimal place for accurate comparison.

genotype (G/G). Age, duration of the disease, years of therapy with L-dopa, L-dopa equivalent daily dose (LEDD), and baseline UPDRS (Parts I, II, III, and IV), CGI, ADL, and H&Y scores did not differ significantly between the three groups of patients. The taking of entacapone significantly improved the UPDRS score, "on" and "off" durations, ADL, CGI, and H&Y stage regardless of the COMT gene subtype. The entacapone dose across all groups was 489.3±176.1 mg/day, and did not differ among the three genotypes.

The plasma samples in which 3-OMD was measured were separated within 2 hours after blood sampling in 195 blood samples (60.4%). The mean interval between blood sampling and plasma separation was 4 hours. The measured 3-OMD level did not differ between immediate-separation cases (less than 1 hour) and delayed-separation cases (more than 3 hours).

The plasma concentration of 3-OMD was 2445±2110 ng/ml at baseline and 1355.7±1454.6 ng/ml after 8 weeks of entacapone treatment. The reduction in 3-OMD plasma level was similar in the three COMT genetic groups (Table 3). The entacapone dose was correlated with the reduction in 3-OMD (r=0.206, $p<0.012$).

Table 3: 3-OMD level vs COMT genotype

	G/G	G/A	A/A	Total
Baseline	2513.6±2501.6	2354.5±1975.3	2493.7±2808.4	2445.0±2110.4
2 months later	1328.1±1436.1	1287.5±1356.0	1696.2±1852.4	1355.7±1454.6
Difference	1130.1±1295.6	1067.0±1270.3	797.5±1813.7	1063.2±1351.2

Values are expressed as mean ± standard deviation. (in ng/ml).

Table 4: Adverse events

Adverse event	First visit (1 month later)	Second visit (2 months later)
Dyskinesia	12	13
Aggravation of PD symptom	4	3
Dry mouth or eye	4	5
Headache	1	2
Dizziness	1	1
Vivid dreaming	1	0
Gastrointestinal discomfort	1	2
Constipation	2	0
Nausea	3	1
Agitation, anxiety	2	0
Paresthesia/itching	1	1
Visual hallucination	0	1
Stiffness	0	2
Myalgia	0	1
Fatigue	0	1

Data are the number of patients

Adverse events occurred in 4 of the 19 $COMT^{AA}$ patients, 15 of the 68 $COMT^{GA}$ patients, and 22 of the 81 $COMT^{GG}$ patients. Dyskinesia was the most common adverse event (26.6%). The frequency and duration of dyskinesia and the frequencies of other adverse events did not differ significantly with the COMT genotype. The frequencies of other side effects are listed in Table 4.

DISCUSSION

This study demonstrated that COMT inhibition with entacapone treatment in patients with short wearing-off periods significantly improved motor function, as measured by the "off" duration and ADL and UPDRS scores. The benefits occurred in all three COMT genotype groups, without any differences in the frequency or duration of dyskinesia.

We recruited PD patients with short wearing-off periods with the aim of ensuring, that our patient population was in earlier stages of the disease than those patients included in previous studies, and thus less encumbered by problematic dyskinesia. Comparison of the demographic data between our study and the previous study[15,17] revealed that our population had a shorter duration of the disease (6.6 vs 7.9–11.6 years) and less-severe motor function as judged by the UPDRS Part III score (17.9 vs 21.4–25.8). As we anticipated, the frequency of dyskinesia in our population was also lower (19.6% vs 26.2%). The 3-OMD concentration reflects the shunting of L-dopa to 3-OMD, and the degree of reduction in the 3-OMD concentration indicates the degree of inhibition by COMT inhibitors, and thus the increase in available L-dopa. Entacapone induced a significant reduction in the plasma level of 3-OMD. We hypothesized that the COMT genotype would be correlated with the degree of reduction in 3-OMD induced by entacapone. However, this was found not to be the case, and the clinical outcomes and adverse events did not differ significantly among

the three genotypes. Recent study demonstrated that the high activity COMT genotype increased the positive effect of entacapone on the response of PD patients to L-dopa.[18] And also, entacapone-induced changes in the biodisponibility of L-dopa were enhanced in high activity group. However, this trial evaluated the efficacy of entacapone in acute challenge of L-dopa, which could not reflect chronic effect in clinical field. In addition, considering the participants were mainly Caucasians, the racial differences might be a factor of contrary results.

In summary, the present study found no association between COMT genotype and the efficacy or side effects of COMT inhibitors in PD patients who experienced motor fluctuations of ≤2 hours. The decrease in 3-OMD level at 2 months after COMT inhibitor administration was similar across all COMT polymorphisms.

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