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Daily dose of dopaminergic medications in Parkinson disease: Clinical correlates and a posteriori equation

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Abstract

Objectives: To survey daily doses of dopaminergic medications and to draw a posteriori equation of the dose in relation to the various clinical variables in Korean patients with Parkinson disease. *Methods:* A multi-center cross-sectional survey was conducted over a defined period. Information on patient demographics and clinical features including age at Parkinson disease onset, disease duration, treatment duration and Hoehn and Yahr stage, and daily doses of anti-parkinsonian drugs was obtained from the patients' medical records. *Results:* A total of 1,762 patients with Parkinson disease were recruited from 6 referral centers. The mean L-dopa equivalent daily dose (LEDD) in the whole population was 608.9 mg/day, which tended to increase linearly depending on the duration of disease and Hoehn and Yahr stage. LEDD was also significantly affected by age and gender. We performed multiple linear regression analyses and devised a posteriori equation of LEDD with clinical variables.
Conclusions: This survey provides systematic data for mean LEDD in Korean Parkinson disease patients. In spite of profound individual variations in LEDD, our linear regression model provides an insight about the relationship between daily doses of dopaminergic medications and various clinical features of Parkinson disease.

INTRODUCTION

The treatment of Parkinson disease (PD) is an individualized process based on symptom severity, individual needs, and benefits and side effects of the drugs. Due to the diversity of clinical and socioeconomic factors amongst patients, it is understandable that there are major differences in the practical use of dopaminergic medications.

It came to our attention that the preoperative L-dopa equivalent daily dose (LEDD) in our patients who underwent bilateral subthalamic nucleus (STN) deep brain stimulation (DBS)[1] was much smaller than that reported in studies from Europe and North America (808.5 vs. 1074-1409 mg/day)[2-5], even though presurgical conditions such as mean duration of disease and UPDRS score were similar. Interestingly, the preoperative LEDDs in studies conducted in Asian populations were also relatively small (Taiwanese 788.8 and 899.9 mg/day[6] and Japanese patients 419.5 mg/day[7]). Thus, we suspected that there might be an ethnic difference in the LEDD in PD. This hypothesis was also suggested in a clinical trial of zonisamide involving Japanese PD patients.[8] The authors postulated that differences in protein intake and/or other cultural differences may account for lower LEDD in Asian patients compared with Caucasians.[8] However, so far there is little systematic data for LEDD in relation to clinical features of PD in any ethnic population, and the LEDD in different populations may not be directly compared unless adjusted for differences in demographics of study subjects, duration and severity of PD, and preferred prescribing patterns of anti-parkinsonian medications which may be affected by the economic and cultural environment of the society.

Thus we conducted a multicenter cross-sectional survey of the use and daily dosages of anti-parkinsonian drugs in Korean PD patients

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over a defined 4-month period and investigated the relationship between LEDD and the clinical features of patients with PD.

METHODS

Study population

The survey was conducted in 7 movement disorder centers, all of which were referral hospitals. Dong-A University Medical Center (DAUMC) is located in Busan, and the other hospitals are located in Seoul. Patients who (1) visited the movement disorder clinic at each hospital between September 2007 and December 2007, (2) were clinically diagnosed with PD according to the criteria of the UK PD Society Brain Bank[9] and (3) had been followed up for more than 6 months after diagnosis were eligible for study participation. This survey also included 92 patients who underwent STN DBS and had been followed up during the study period, in order to avoid omitting advanced cases. In these cases, information concerning the preoperative condition was used. Rare patients with previous surgical treatment other than STN DBS were excluded. The Institutional Review Board (IRB) approved this study.

Data collection

Data were collected from patients' medical records and interviews. The items consisted of age at the time of visit, gender, age at PD onset, body weight, height, and duration of disease. Data concerning the Hoehn and Yahr (HY) stage and daily doses of anti-parkinsonian medications, including L-dopa, dopamine agonists, a COMT inhibitor (entacapone), a MAO-B inhibitor (selegiline), amantadine and anticholinergics, were also collected. In patients with motor fluctuations, HY stage was rated in a "practically defined" off-medication state (i.e., at least 12 hours after the last dose of dopaminergic medication).

Data analysis

We determined the total daily dose of dopaminergic medications in each patient by means of a L-dopa equivalent daily dose (LEDD, mg/day). This was calculated from the dosages of administered dopaminergic drugs based on theoretical equivalence as previously reported,[1-5,10,11] as follows: 100 mg of L-dopa = 130 mg of L-dopa in controlled-release form = 77 mg L-dopa with entacapone = 1 mg pergolide = 1 mg pramipexole = 5 mg ropinirole = 10 mg bromocriptine. Body surface area (BSA) was calculated as [height (cm) × body weight (kg)/3600]$^{1/2}$ by the Mosteller formula.[12]

We plotted the LEDD according to the duration of the disease and HY stage. Clinical variables, such as body weight, BSA, gender, age, age at PD onset, disease duration, and HY stage were examined to see whether they significantly correlated with LEDD by Pearson's method. Variables with significant correlation at the level of 0.01 were used in the multiple linear regression analysis.

We used t-test in the comparisons of LEDD and HY stage between the subgroups described in the result section. Statistical analysis was conducted using SPSS software version 12.0 (SPSS Inc., Chicago IL), with the limit of significance set at 0.05 (two-tailed).

RESULTS

A total of 1,762 patients (773 male, mean age 65.1 ± 9.9 years, range 23-91 years) were included in this study. Information on body weight and height was obtained in 1,554 patients. The clinical characteristics of the included patients are summarized in Table 1.

The mean LEDD was 608.9 ± 381.8 mg/day, and it was lower in females than in males (572.3 ± 359.4 vs. 655.8 ± 404.2 mg/day, respectively, $p<0.001$). The mean daily dose of L-dopa was 487.5 ± 338.6 mg/day, and the mean daily doses of dopamine agonists were 8.5 ± 5.0 (bromocriptine), 1.0 ± 0.5 (pergolide), 4.9 ± 3.4 (ropinirole) and 2.1 ± 1.6 mg/day (pramipexole). The frequency of individual dopamine agonist use is shown in Table 1. Entacapone was used in 20.4% of patients (mean dose of 474.1 ± 200.6 mg/day). There was no difference in mean LEDD according to the use of selegiline and amantadine ($p=0.841$ and 0.835, respectively), while the mean LEDD was significantly lower in patients taking anticholinergics (509.1 ± 340.1 vs. 629.9 ± 386.9 mg/day, $p<0.001$). There was no significant difference in mean HY stage between the patients who were and were not taking selegiline ($p=0.155$), while the mean HY stages in the patients who were taking amantadine or anticholinergics were significantly lower than those in patients who were not taking amantadine (2.3 ± 0.8 vs. 2.5 ± 0.8, $p<0.001$) or anticholinergics (2.3 ± 0.8 vs. 2.4 ± 0.8, $p=0.013$). The profile of anti-parkinsonian drugs administered is shown in Table 1.

Most (90.4%) of the patients took L-dopa, and about 68% took dopamine agonists. The most

Table 1: Clinical characteristics of patients (n=1,762) and the profile of administered anti-parkinsonian drugs.

Characteristics	Value
Gender (M/F)	773/989
Age (years)	65.1±9.9 (23-91)
Body weight[a] (kg)	59.6±9.7
Height[a] (cm)	160.7±8.5
Body surface area[a,b] (BSA, m^2)	1.6±0.2
Hoehn and Yahr (HY) stage (0-5)	2.4±0.8
Duration of PD (years)	6.3±4.3 (0.6-33)
Age at PD onset (years)	58.7±10.7 (18-85)
Duration of treatment with $_{L}$-dopa[c] (years)	4.5±4.0 (0.1-29)
Duration of treatment with dopamine agonist[d] (years)	3.9±3.3 (0.1-22)
L-dopa equivalent daily dose[e] (LEDD, mg/day)	608.9±381.8
L-dopa (%)	90.4
Dopamine agonist (%)	68.1
Bromocriptine	4.2
Pergolide	0.4
Ropinirole	41.6
Pramipexole	21.2
Pattern of dopaminergic therapy (%)	
L-dopa monotherapy	29.2
L-dopa + agonist	61.2
Agonist monotherapy	6.9
No dopaminergic drugs	2.7
Entacapone (%)	20.4
Selegiline (%)	26.2
Amantadine (%)	42.0
Anticholinergics (%)	17.4

Values are shown as percentages or mean ± standard deviation (range).
[a]calculated in 1554 patients; [b]BSA=([height(cm)×weight(kg)]/3600)$^{1/2}$ by the Mosteller formula; [c]available in 1,729 patients; [d]available in 1,135 patients; [e]LEDD was calculated from the dosages of administered dopaminergic drugs based on theoretical equivalence (see text).

frequent pattern was a combination of dopamine agonist and L-dopa (61.2%), followed by L-dopa monotherapy (29.2%). A total of 121 (6.9%) patients received dopamine agonist monotherapy, and 48 (2.7 %) took neither L-dopa nor dopamine agonists. Seven of the 48 patients were not treated with any medication, while the others were treated with amantadine, selegiline and/or anticholinergic therapy. The pattern of therapy according to HY stage is depicted in Figure 1.

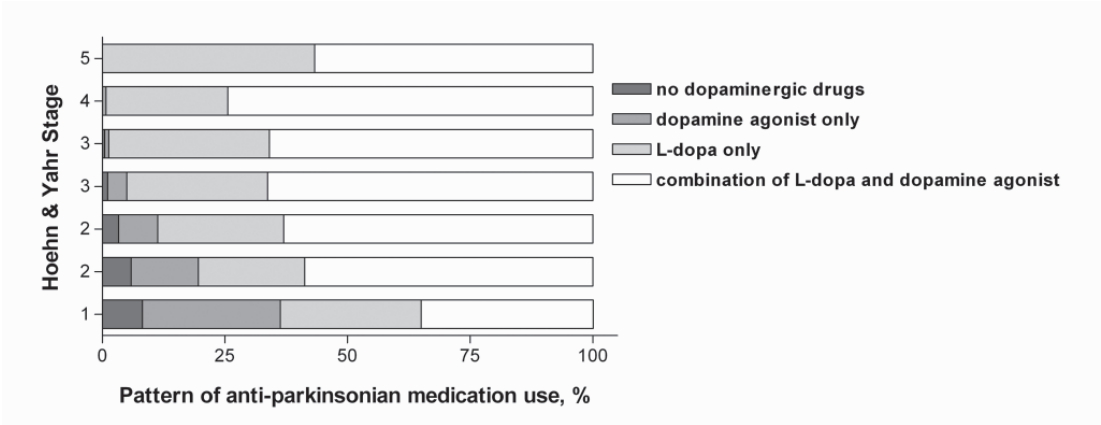

Figure 1. Pattern of dopaminergic therapy in Korean patients with Parkinson's disease according to Hoehn and Yahr stage.

The relationships between LEDD and the duration and severity of PD

To examine the relationship between LEDD and duration of PD, we plotted the LEDD according to the duration of PD (Figure 2A). The disease duration was 10 years or less in most (1,536, 87.2 %) patients. The LEDD correlated positively with the duration of PD, but there was a very wide range of LEDD (Figure 2A). Figure 2B shows the mean LEDD plotted against the duration of disease; the mean LEDD increased almost linearly according to the duration of disease until it reached about 10 years, at which point the mean LEDD plateaued and even decreased (Figure 2B). The same pattern was observed when the data from each center was plotted separately. When the mean LEDD was plotted according to HY stage, a linear increase was observed up to stage 4, and it tended to decrease at stage 5 (p=0.050, for comparison of mean LEDD between HY 4 and HY 5 groups by t-test, see Figure 3). There was a very wide range of LEDD in each HY stage.

A posteriori equation for LEDD

We constructed a multiple linear regression equation to compare LEDD among various patient populations. Data from the patients (n=1,506) with disease duration of 10 years or less and HY stage of four or less were considered in the regression analysis because patients with advanced PD are likely to have cognitive dysfunction which tends to limit the use of antiparkinsonian medications as seen in Figures 2 and 3. With LEDD as the dependent variable, the following variables were

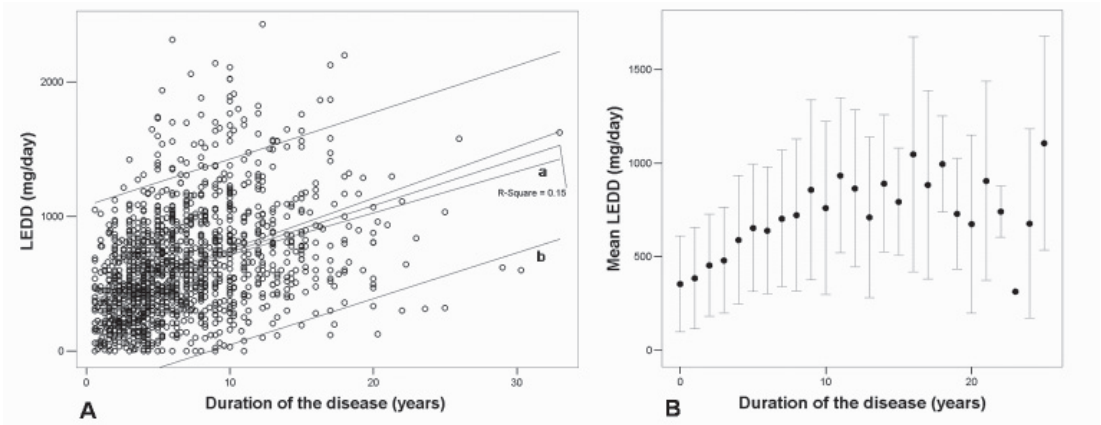

Figure 2. Scattergram of the relationship between the L-dopa equivalent daily dose (LEDD) and disease duration (A), and plot of mean LEDD for each year of the disease (B) in 1762 patients. (A) A simple linear regression line (r^2=0.15) is superimposed, surrounded with the 95% confidence interval (CI) lines for the regression line (a), and by CI for the individual predicted values (b). (B) An error bar shows standard deviation. The dot at the right end represents the mean LEDD of patients with disease duration of 25 years or more.

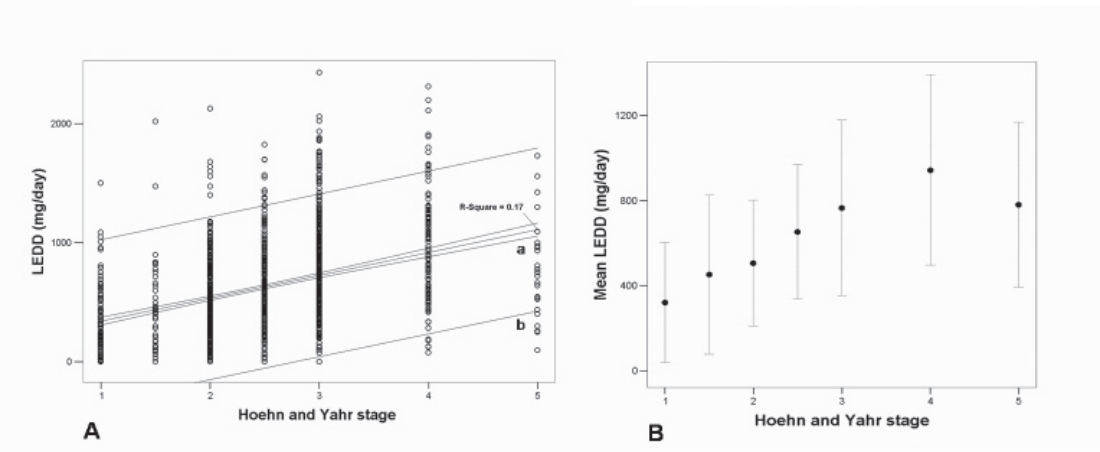

Figure 3. Scattergram of the relationship between the L-dopa equivalent daily dose (LEDD) and Hoehn & Yahr (HY) stage (A), and plot of mean LEDD for each HY stage (B) in 1,762 patients. (A) A simple regression line (r^2=0.17) is superimposed, surrounded with the 95% confidence interval (CI) lines for the regression line (a), and by CI for the individual predicted values (b). (B) An error bar shows standard deviation. The mean LEDD is lower at HY stage 5 than at HY stage 4 with marginal significance (p=0.050, by t-test).

entered as covariates: HY stage in off-medication state, duration of PD, gender, current age and age at PD onset. BSA and bodyweight were not included in the analysis because they were not significantly correlated with LEDD by Pearson's method. During the regression analysis, age at onset was excluded due to lack of significance in the final regression model. The final equation (adjusted R square = 0.27, F=137.60, p<0.0001) is as follows: LEDD = 237.35 + 172.69 × (HY stage in off-medication state) + 35.51 × (duration of PD in years) – 3.30 × (age in years) – 45.97 (if female gender). A summary of the proposed multiple linear regression model for the LEDD in Korean patients with PD is shown in Table 2. As seen in this model, HY stage seemed to have the largest impact on the daily dose of dopaminergic medications, followed by disease duration (see the coefficient beta, Table 2).

DISCUSSION

In this survey, we estimated the daily dose of dopaminergic medications in terms of LEDD in Korean patients with PD and derived a posteriori equation of LEDD with clinical variables including HY stage, disease duration, age and gender. Although there was no good data for direct comparison in regards to ethnic differences, the mean LEDD (608.9mg/day) in Korean PD patients

Table 2: A proposed multiple linear regression model for LEDD in Korean patients with Parkinson's disease

Variables	Regression Coefficient	coefficient β	SE	95% CI	t-value	*p*-value
Intercept	237.35		56.51	126.50 to 348.21	4.20	<0.0001
HY stage, 1-5	172.69	0.34	12.67	147.85 to 197.54	13.63	<0.0001
Female gender	–45.97	–0.06	16.31	–7.96 to –13.98	–2.82	0.0049
Disease duration, yr	35.51	0.27	3.15	29.32 to 41.69	11.26	<0.0001
Age, yr	–3.30	–0.09	0.84	–4.95 to –1.65	–3.93	0.0001

Abbreviations as for Table 1. SE=standard error; CI=confidence interval.
Adjusted R^2 =0.27 and F=137.60, p<0.0001 for this model. The *p*-values are two-tailed.

seemed to be not so different from that reported in a German study (599.15 mg/day)[13], which was designed to analyze prescribing patterns in the nation. In the German study, the clinical characteristics of the study population such as the distribution of duration and severity of PD were not clearly described, and the study was based largely on office-based neurologists (87%), whereas ours was based on referral hospitals, thus direct comparison of the LEDD between the two studies may not be appropriate due to methodological and population differences.

LEDD and factors affecting pharmacokinetics of dopaminergic drugs

Among the demographic factors, BSA and body weight were not significantly correlated with LEDD by Pearson's correlation (p=0.104 and p=0.137), which might be attributable to the narrow range and little variation in these factors in our population (shown in Table 1). A slight male predominance in PD frequency has been suggested by many record- and clinic-based studies as well as by one prospective cohort study in Italy.[14] In contrast to this, we observed a female preponderance (about 1.3:1) in our Korean PD population; this finding needs to be verified by prospective cohort studies in the future. The LEDD tended to be lower in older patients and in females, which may be related to differences in the pharmacokinetics of dopaminergic drugs.[15,16]

LEDD varies according to the duration and severity of the disease

There was great variation in LEDD for each year of the disease as well as for each HY stage (Figures 2 and 3), which reflects that the individual needs of each patient vary greatly. Despite the wide variation, the mean LEDD tended to increase until the duration of disease reached about 10 years, but varied widely after that. We suspect that L-dopa-related motor and neuropsychiatric complications may hamper further increases in the dose of L-dopa and dopamine agonists in advanced PD. The mean LEDD was lower in patients in HY stage 5 than in those in HY stage 4 (Fig. 3), which was also seen in the German report.[13]

As seen from the equation, the LEDD tended to increase with longer disease duration, higher HY stage, whereas it tended to decrease with older age and female gender. It should be stressed that the adjusted R square of the finally adopted regression equation was relatively low (0.27) and this a posteriori equation would not predict a standardized dosage in individual patients. Nonetheless, the equation may be helpful for roughly estimating the daily requirement for dopaminergic medications in relation to the demographic and clinical features of patients.

The pattern of drug therapy and its contribution to LEDD

The combination of $_{L}$-dopa and dopamine agonists (61.2%) was the most frequent, followed by L-dopa monotherapy (29.2%) and dopamine agonist monotherapy (6.9%). A seven-country survey reported that the frequency of agonist monotherapy was about 15% in Japan and about 25% in Europe and the USA, and the frequency of combination therapy was 56% in Japan, 40% in Europe and 35% in the USA.[17] The rate of dopamine agonist monotherapy was the lowest and of combination therapy was the highest in Korea.

The use of MAO-B inhibitors, amantadine and anticholinergics in Korea was similar to that in Germany.[12] There was no difference in mean LEDD between the subgroups of patients who were or were not taking selegiline or amantadine. The mean HY stage did not differ according to the use of selegiline, and it was lower in patients taking amantadine. Although selegiline and amantadine have antiparkinsonian effects, the L-dopa-sparing effect appears to be very small. It is interesting to note that the mean LEDD was lower in anticholinergic users, which probably reflects a tendency towards prescription of anticholinergics in patients with tremor-dominant parkinsonism and avoidance of anticholinergics in advanced PD patients who are at risk for dementia.[18]

Our study has several limitations. First, it was a referral hospital-based survey, and not community-based, which may have led to the inclusion of more severe cases. Second, all of the participating hospitals, except DAUMC, were located in Seoul, the largest city in Korea, thus a selection bias was not completely excluded. However, owing to the well-developed transportation system in Korea, many patients in distant areas come to the major centers in Seoul for treatment, which can lower the selection bias. Third, this was a retrospective study, and the onset of symptoms was mostly dependent on patient memory. Thus, the actual disease duration might be longer than that recollected by patients. Fourth, construction of a linear regression model from a cross-sectional survey had some limitation for generalization even though a large sample size fulfilling the criteria of normal distribution

sufficiently raised the statistical power of the analysis. Fifth, the dopaminergic potency of the agonists was determined by a formula from the literature which has been widely used in practice, however this simple mathematical conversion has unavoidable limitations since there are differences in pharmacokinetic and pharmacodynamic properties among the drugs which cannot be directly compared by dosage alone.

In conclusion, we showed that the daily dose of dopaminergic medication was positively correlated with the duration and severity of PD, and we devised a posteriori equation of the dose. This survey also provided systematic data for mean LEDD in a large cohort of Korean patients with PD, and the pattern of use of anti-parkinsonian medications in Korea. The LEDD may be affected by many factors such as medical and socioeconomic policies, cultural tendencies, medical insurance systems of the society, prescribing patterns of physicians, and inherent ethnic differences as well as the clinical features of PD. We think that our data for LEDD in the Korean population may be a reflection of the sum of these factors. It is suggested that similar studies are worth conducting in other countries to provide data for future comparisons of mean LEDD in PD patients of varying ethnic populations.

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The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

The authors have no conflict of interest.

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