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Journal of Neurological Disorders & Stroke

Research Article

Special Issue on
Parkinson's Disease

Motor and Non-Motor Symptoms of 1453 Patients with Parkinson's Disease: Any Relationship with the Cumulative Doses of Anti-Parkinsonian Medications?

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Submitted: 28 December 2013

Accepted: 14 January 2014

Published: 16 January 2014

Keywords
- Parkinson's disease
- Wearing-off
- Camptocormia
- Sleep attack
- Psychosis
- Pneumonia
- Cumulative dose

Abstract

Background and Purpose: We examined the prevalence of clinical symptoms and cumulative dose of anti-parkinsonian drugs in Japanese patients with Parkinson's disease (PD).

Methods: We retrospectively reviewed the charts of patients (n = 1453; 650 males) who had visited our outpatient neurology clinic between January and June 2010. Cumulative dose was calculated by calendar day to the day of onset of events, or the day of the examination. Prevalence and risk of events (pain, wearing-off, camptocormia, sleep attack, orthostatic hypotension, psychosis, and pneumonia) were analyzed using Kaplan–Meier survival curves, calculated odds ratios, and hazard ratios (HRs).

Results: Most patients (1292, 88.9%) received levodopa, and the cumulative dose was 1263 (SD 1190) g. Moreover, 1182 patients (81.3%) received dopamine agonists (DAs; average cumulative dose, 827 (1466) g. The cumulative doses of trihexyphenidyl (n = 561), amantadine (n = 598), and selegiline (n = 620) were 8246.1 (11156.7) mg, 386.5 (829.2) g, and 7587.4 (11006.9) mg, respectively. The HRs were as follows: 0.998 ($p < 0.001$) for the cumulative dose of levodopa to the onset of pain, wearing-off, camptocormia, and psychosis; 0.997 ($p < 0.001$) for the cumulative dose of levodopa to the onset of orthostatic hypotension; 0.999 ($p < 0.001$) for the cumulative dose of DAs to the onset of camptocormia; and 0.999 ($p < 0.001$) and 0.999 ($p < 0.05$) for the cumulative doses of levodopa and DA to the onset of pneumonia. However, the HRs were close to 1.0.

Conclusions: There was no relationship between the cumulative dose of anti-parkinsonian drugs and the prevalence of symptoms.

ABBREVIATIONS

PD: Parkinson's Disease; OR: Odds Ratio; HR: Hazard Ratio; DA: Dopamine Agonist; H& Y Hoehn and Yahr; K-M: Kaplan–Meier; SD: Standard Deviation; CI: Confidence Intervals; LCD: Larger Cumulative Dose; SCD: Smaller Cumulative Dose

INTRODUCTION

Dopamine replacement with levodopa, dopamine agonists (DA), or non-dopaminergic drugs can result in the marked improvement of motor symptoms and alleviation of disability in Parkinson's disease (PD); these treatments have also improved patient survival [1,2]. However, the debate over the role of levodopa in the treatment of PD was increased by in vitro studies that showed the generation of free radicals by levodopa and its toxic effects in cell culture [3,4], and non-toxic effects in vivo [4]. Cumulative dose and symptoms were examined especially in heart valve regurgitation using ergot-derived DA. Here, we have described the prevalence of clinical symptoms and risks associated with the cumulative dose of the drugs in a large number of Japanese patients with PD. This article reports prevalence, odds ratio (OR), and hazard ratio (HR) of cumulative dose efficacy and tolerability.

PATIENTS AND METHODS

The cohort of this report was the same as our previous report [5]. Between January and June 2010, we retrospectively reviewed

the charts of patients who had visited our outpatient neurology clinic at Juntendo Hospital in Tokyo, and had been diagnosed with PD by a board-certified neurologist. Diagnoses were based on the UK Brain Bank diagnostic criteria for PD [6]. Patients with dementia with Lewy bodies [7], progressive supranuclear palsy, corticobasal degeneration, vascular parkinsonism, or other forms of parkinsonism were excluded. Hospital charts were systematically reviewed by A. Y. This study was approved by the Juntendo Hospital institutional ethics committee, and informed consent was obtained. The patients with PD in this study, and the criteria of "Onset," "Pain," "Camptocormia," "Sleep Attack" [8], "Orthostatic hypotension," and "Psychosis" [9] were the same as our previous study [5]. The daily levodopa-equivalent dose was calculated on the basis of the following equivalences: 100 mg standard levodopa = 10 mg bromocriptine = 1 mg pergolide = 5 mg ropinirole = 1 mg pramipexole [10]. Cumulative dose was calculated by calendar day to the onset of the events or if not, to the examined day, and excluded the dose amounts of forgotten medications or short interruptions caused by examinations or other treatments. The cumulative dose before the patients came to our hospital was calculated as follows. For levodopa, if patients forgot their exact daily dose before coming to our hospital, we calculated a trapezoidal area where one side was set to 300 mg as a commencement daily dose and the other side would be the dose for the first day of the visit at our hospital × (duration from the drug commencement year to the first year in our hospital (integer number)) × 365, if the dose of the first day at our hospital was under 300 mg, the dose of the commencement day × (the duration from the drug commencement year to first year in our hospital (integer number)) × 365. Other drugs were calculated by the dose on the patients first visit to our hospital × (duration from the drug commencement year to first year in our first hospital (integer number)) × 365.

STATISTICAL ANALYSES

SPSS (ver. 20; SPSS Inc. , Chicago, IL, USA) was used for statistical analyses. The data are presented as mean (standard deviation [SD]) values for age, age at onset, Hoehn and Yahr (H & Y) stage of the "on" phase, daily dose or cumulative dose of the drugs, and duration from the onset of PD for important events. H & Y stages without parkinsonian symptoms in the "on" phase were considered as "0. " Point prevalences were calculated, and Kaplan–Meier (K–M) time-to-event curves and log-rank tests were used to estimate the absolute risk of each event. Logistic regression was performed to calculate ORs with 95% confidence intervals (CIs) for each event. The factors chosen were as follows: age at onset, age, sex, H & Y stage, and cumulative doses. Cox proportional-hazard modeling was used to calculate HRs and 95% CIs for differences among subgroups embedded into the following variables: age at onset, sex, duration to the start of drugs (levodopa, other drugs, or all anti-parkinsonism drugs), and the cumulative dose to the onset of events. Statistical tests were two-sided, and the significance level was set at $p < 0.05$.

RESULTS

We evaluated 1453 patients with PD (650 males). Their mean age (SD) was 67.7 (10.0), age of onset was 58.1 (11.5), and disease duration was 9.7 (6.6) years. The mean follow-up at our hospital was 5.9 (5.7) years. The mean H & Y stages were 2.2 (0.8) at the first visit and 2.8 (1.2) at the final evaluation. Patients with H & Y stages 0, I (0.5 and 1.0), II (1.5 and 2.0), III (2.5 and 3.0), IV (4.0), V (5), and unknown (not described) were 3.3%, 7.0%, 29.5%, 30.1%, 20.2%, 6.8%, and 1.7%, respectively.

Most patients (1292, 88.9%) received levodopa, and the average daily dose at enrollment was 547.7 (257.6) mg/day, and the cumulative dose was 1263 (1190) g. In total, 1182 patients (81.3%) also received DAs; the average equivalent dose at enrollment was 136.2 (140.7) mg/day, and the cumulative dose was 827 (1466) g. Entacapone and zonisamide were not examined, because the use of these medications has only recently started in Japan. The cumulative dose of pramipexole (n = 899) was 2473.9 (4640.1) mg. Ropinirole (n = 212), pergolide (n = 414), cabergoline (405), trihexyphenidyl (n = 561), amantadine (n = 598), and selegiline (n = 620) were 4672.4 (4705.1) mg, 2080.8 (1982.0) mg, 3664.5 (6870.0) mg, 8246.1 (11156.7) mg, 386.5 (829.2) g, and 7587.4 (11006.9) mg, respectively.

The cumulative doses of levodopa, DA, trihexyphenidyl, amantadine, and selegiline were correlated with disease duration (r = 0.833, 0.393, 0.585, 0.533, and 0.327, respectively; Spearman's correlation coefficient; $p < 0.001$). The cumulative dose of each drug was categorized into one of three groups: a larger cumulative dose (LCD) group, a smaller cumulative dose (SCD) group, and a non-medicated group. The LCD group used over 1000 g of levodopa, 300 g of total DAs, 5000 mg of trihexyphenidyl, 200 g of amantadine, or 5000 mg of selegiline. The SCD group showed a cumulative dose of each of the drugs that was less than the value of the LCD group (e. g. , levodopa dose < 1000 g, DAs < 300 g, etc.). Depending on the elapsed time from disease onset to the start of drug administration, the patients were divided into two groups by either early or late start, based on the criterion of their third year on levodopa, 4th year on DAs and trihexyphenidyl, 5th year on amantadine, or 6th year on selegiline. The prevalence and mean duration of each symptom from the onset of PD are shown in a previous report [5]. Logistic regression and Cox HRs are shown in Tables 1 and 2, respectively.

Pain

About 23.4% of patients had pain at a mean duration of 6.94 (5.12) years from PD onset. The early start groups for all examined drugs showed significantly different prevalence (levodopa, DA, and selegiline: $p < 0.001$; trihexyphenidyl: $p < 0.05$; amantadine: $p < 0.01$). For all examined drugs, the LCD group showed lower symptom prevalence than the SCD group ($p < 0.001$). Logistic regression showed that the OR of pain was not statistically significant for cumulative dose (Table 1). Cox modeling revealed that the duration to the start of levodopa and the cumulative dose of levodopa were associated with a decreased HR of pain (Table 2).

Wearing-off

About 44.7% of patients experienced wearing-off an average of 7.52 (4.66) years after PD onset. Duration to the start of trihexyphenidyl and amantadine showed no effect on the prevalence of wearing-off, and all other drugs led to a higher prevalence in the early start groups (levodopa and DA: $p < 0.001$; selegiline: $p < 0.01$). The LCD group of all examined

Table 1: Logistic regression of the events in patients with Parkinson's disease.

Events	Statistical analysis	Age at onset	Age	Sex (female)	H & Y stage	CD of levo-dopa	CDof total dopamine agonist	CD of trihexyohenidyl	CD of aman-tadine	CD of selegiline
Pain	odds ratio	0.515	1.943	1.135	NE	1.000	1.000	1.000	1.000	1.000
	CI	0.467-0.567	0.762-2.142	0.843-1.528		1.000-1.000	1.000-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001 ***	<0.001 ***	0.403		0.205	0.145	0.555	0.577	0.842
Wearing-off	odds ratio	0.929	NE	1.894	NE	1.000	1.000	1.000	1.000	1.000
	CI	0.918-0.940		1.485-2.415		1.000-1.000	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001 ***		<0.001 ***		0.040*	<0.001 ***	0.540	0.060	0.013*
Camptocormia	odds ratio	0.967	NE	1.642	1.561	1.000	0.999	1.000	1.000	1.000
	CI	0.951-0.984		1.129-2.387	1.313-1.855	1.000-1.001	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001 ***		0.009**	0.001**	0.005**	0.001*	0.492	0.509	0.446
Sleep attack	odds ratio	0.623	1.375	0.026	19.33	0.997	0.999	1.000	1.000	1.000
	CI	0.336-1.155	0.727-2.603	0.001-1.251	1.300-287.435	0.992-1.001	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.133	0.327	0.065	0.032	0.112	0.349	0.741	0.144	0.230
Orthostatic hypotension	odds ratio	0.89	1.129	NE	1.266	0.999	1.000	1.000	1.000	1.000
	CI	0.854-0.926	1.078-1.183		1.014-1.581	0.999-1.000	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001 ***	<0.001 ***		0.038*	<0.001 ***	0.028*	0.886	0.995	0.995
Psychosis	odds ratio	0.881	1.143	1.064	1.448	0.999	1.000	1.000	1.000	1.000
	CI	0.856-0.908	1.105-1.182	0.828-1.369	1.274-1.645	0.999-0.999	0.999-1.00	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001 ***	<0.001 ***	0.627	<0.001 ***	<0.001 ***	<0.001 ***	0.918	0.340	0.839
pneumonia	odds ratio	0.927	1.114	0.665	2.571	1.000	0.999	1.000	1.000	1.000
	CI	0.874-0.984	1.038-1.195	0.382-1.158	1.857-3.558	0.999-1.000	0.989-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.012*	0.003**	0.149	<0.001 ***	0.255	0.027*	0.017*	0.052	0.903

H & Y: Modified Hoehn and Yahr, CD: cumulative dose, CI: confidence interval, *: p < 0.05 , **: p < 0.01, ***: p < 0.001, NE: not examined.

Table 2: Cox proportional hazards models for clinical events in PD patients.

Events	Statistical analysis	Age at onset	Sex (female)	Duration to start of levodopa	Duration to start of the drugs except levo-dopa	Duration to start of the first anti-parkinso-nian drugs	CD of levo-dopa to the onset of events	CD of dopamine agonist to the onset of events	CD of trihex-iphenidyl to the onset of events	CD of amanta-dine to the onset of events	CD of sel-egiline to the onset of events
Pain	HR	0.995	0.905	0.788	0.964	0.972	0.998	1.000	1.000	1.000	1.000
	95%CI	0.984-1.006	0.720-1.138	0.735-0.845	0.923-1.006	0.885-1.068	0.998-0.999	1.000-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.408	0.395	<0.001***	0.090	0.552	<0.001***	0.386	0.036*	0.226	0.018*
Wearing off	HR	0.972	0.978	0.779	0.980	0.982	0.998	1.000	1.000	1.000	1.000
	95%CI	0.965-0.979	0.827-1.157	0.741-0.818	0.953-1.007	0.924-1.043	0.998-0.999	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001***	0.798	<0.001***	0.140	0.548	<0.001***	<0.001***	0.001**	0.008*	0.078
Camptocormia	HR	0.985	1.494	0.721	0.840	1.072	0.998	0.999	1.000	1.000	1.000
	95%CI	0.969-1.002	1.051-2.122	0.641-0.810	0.767-0.920	0.912-1.260	0.998-0.999	0.998-0.999	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.076	0.025*	<0.001***	<0.001***	0.402	<0.001***	<0.001***	0.001	0.475	0.256
Sleep attack	HR	0.989	0.490	0.875	0.732	1.252	1.000	1.000	1.000	1.000	1.000
	95%CI	0.963-1.016	0.292-0.820	0.753-1.018	0.615-0.871	0.979-1.601	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.418	0.007**	0.083	<0.001***	0.073	0.016	0.210	0.007**	<0.001***	0.864
Orthostatic hypotension	HR	1.022	0.768	0.665	1.007	0.901	0.997	1.000	1.000	1.000	1.000
	95%CI	0.990-1.056	0.423-1.395	0.546-0.810	0.906-1.121	0.720-1.128	0.996-0.998	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.175	0.386	<0.001***	0.892	0.363	<0.001***	0.137	0.923	0.636	0.273
Psychosis	HR	1.003	0.721	0.741	1.018	0.996	0.998	1.000	1.000	1.000	1.000
	95%CI	0.996-1.017	0.585-0.890	0.696-0.788	0.982-1.055	0.922-1.076	0.997-0.998	0.999-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	0.246	0.002*	<0.001***	0.324	0.922	<0.001***	<0.001***	0.898	0.028*	0.907
Pneumonia	HR	1.085	0.529	0.778	1.047	1.004	0.999	0.999	1.000	1.000	1.000
	95%CI	1.050-1.121	0.309-0.903	0.659-0.920	0.983-1.116	0.837-1.204	0.998-1.000	0.998-1.000	1.000-1.000	1.000-1.000	1.000-1.000
	p	<0.001***	0.020*	0.003	0.156	0.156	<0.001***	0.041*	0.062	0.193	0.27

CD: cumulative dose, HR: hazard rate, CI: confidence interval, *: p < 0.05 , **: p < 0.01, ***: p < 0.001, NE: not examined.

drugs showed lower symptom prevalence than the SCD group. Logistic regression analysis revealed a significantly higher OR for younger onset age, female sex, and lower cumulative dose of DA (Table 1). Age at onset, the duration to the start of levodopa, and the cumulative dose of levodopa were associated with decreased HRs of wearing-off (Table 2).

Camptocormia

Camptocormia was found in 9.5% of patients an average of 8.05 (6.16) years after PD onset. All drugs except trihexyphenidyl showed significantly higher prevalence in the early start groups (levodopa and amantadine: $p < 0.01$; DA and selegiline: $p < 0.001$). The three cumulative drug dose groups showed significantly different prevalence (levodopa, DA, and trihexyphenidyl: $p < 0.001$; amantadine and selegiline: $p < 0.01$). Logistic regression analysis revealed significantly higher ORs for younger onset age, female sex, higher H & Y stages, and lower cumulative dose of DA ($p < 0.01$). Increased HR of camptocormia was female sex, and decreased HRs were the duration to the start of levodopa, and the drugs except levodopa, and cumulative doses of levodopa and DA (Table 2). In some patients, camptocormia was induced by various drugs, and thus, if the causative drugs were withdrawn, camptocormia might improve. In our study, 34 patients with camptocormia induced by pramipexole had been medicated with 1.75 ± 0.93 mg/day and a cumulative dose of 1173.6 ± 1314.1 mg, which was not a particularly high cumulative dose.

Sleep attack

An average of 8.50 (6.52) years from PD onset, 4.5% of patients had a sleep attack without warning signs. In the early start group, prevalence was significantly higher in selegiline ($p < 0.01$), DA, and trihexyphenidyl ($p < 0.05$) except for levodopa and amantadine. The three cumulative dose groups showed a significantly different prevalence for levodopa and amantadine ($p < 0.001$), DA ($p < 0.05$), and trihexyphenidyl ($p < 0.01$), but not selegiline. Logistic regression analysis revealed no significantly higher ORs (Table 1). Male sex was associated with an increased HR of sleep attack, and duration to the start of levodopa was associated with decreased HR of sleep attack (Table 2)

Orthostatic hypotension

An average of 8.83 (6.04) years from PD onset, 6.5% of patients developed orthostatic hypotension that required treatment. Levodopa, DA, and selegiline showed significantly higher prevalence in the early start group (levodopa and selegiline: $p < 0.01$; DA: $p < 0.05$). The three cumulative dose groups were significantly different in their symptom prevalence (levodopa and DA: $p < 0.001$; trihexyphenidyl, amantadine, and selegiline: $p < 0.01$). Logistic regression revealed that the OR was significantly higher for younger onset age, older age, higher H & Y stages, smaller cumulative dose of levodopa, and DA (Table 1). The duration to the start of levodopa was associated with an increased HR of orthostatic hypotension, and the cumulative dose of levodopa was associated with a decreased HR of orthostatic hypotension (Table 2).

Psychosis

An average of 9.03 (5.38) years after PD onset, about 28.6% of patients had symptoms of psychosis. All drugs except trihexyphenidyl showed a significantly higher prevalence in the early start group ($p < 0.001$). The three cumulative dose groups were significantly different in their prevalence for all drugs ($p < 0.001$). Logistic regression analysis revealed significantly higher ORs for younger onset, older age and higher H & Y stages, and smaller cumulative dose of levodopa and DA (Table 1). Male sex was associated with an increased HR of psychosis, and the duration to the start of levodopa and cumulative dose of levodopa were associated with a decreased HR of psychosis (Table 2). The cumulative dose of trihexyphenidyl and points on the Mini-Mental State Examination had no relation to each other ($R^2 = 0.0164$, data not shown), nor even when this analysis was limited exclusively to elderly patients (>65 years old) ($R^2 = 0.0052$).

Pneumonia

About 4.3% of patients developed pneumonia, which occurred an average of 13.87 (8.04) years after PD onset. Levodopa and selegiline showed a significant higher prevalence in the early start group ($p < 0.001$). LCD group of all drugs except trihexyphenidyl showed lower symptom prevalence ($p < 0.001$). Logistic regression analysis revealed significantly higher ORs for younger onset, older age and higher H & Y stages, and lower cumulative dose of DA (Table 1). Age at onset and male sex were associated with an increased HR of pneumonia, and the cumulative dose of levodopa or DA was associated with a decreased HR of pneumonia (Table 2).

DISCUSSION

In the prevalence of all symptoms, a larger cumulative dose of levodopa was not a risk factor. A controlled trial involving PET studies revealed that levodopa was more likely to be neurotoxic than DAs, but showed better motor activity improvement [11-13]. However, Parkkinen et al. reported that the cumulative dose of levodopa did not correlate to total substantia nigra neural density, and chronic use of levodopa in patients with PD did not enhance the progression of PD pathology [14]. In our study, a larger cumulative dose of levodopa did not induce a higher prevalence of events than did a smaller cumulative dose. The HRs (0.997–0.999) of cumulative doses were very close to 1.0; therefore, the smaller cumulative dose might not appear to be a risk.

Many previous clinical studies have been conducted on levodopa, rasagiline, DAs, and entacapone (Table 3) [15-24]. There was a significant difference in the prevalence of motor complications within 5 years in the delayed start of levodopa, as in the Sydney [18] and 056 studies [21]. Moreover, in our previous uncontrolled study, the duration to the start of levodopa was an important factor [5]. However, over 10 years, there were no differences in the TEMPO [17], Sydney [19], or CALM-PD studies [23]. A larger cumulative dose of levodopa was not a risk factor in our study. Conversely, the prevalence of wearing-off has been related to a higher dose of levodopa [25,26]. In the STRIDE-PD study, factors in the development of wearing-off were age at onset, unified PD rating scale II or III score, nominal levodopa daily dose, female sex, and, in particular, a levodopa dose over the 400 mg/day threshold [27].

We found that female sex, older age at onset, and disease severity were risk factors for camptocormia. The daily dose of

Table 3: The motor complications and survival of the clinical studies and post hoc studies.

Study	n	First stage or double blind	Second stage or open label follow up or total follow up	Drugs	Wearing off (onset) (prevalence)	*p*	Dyskinesia (onset) (prevalence)	*p*	Mortality % survival years death rate	*p*
ELLDOPA study (2004) [15]	311	40 weeks	2 weeks	levodopa 600mg	29.7%	0.06	16.5%	<0.001		
				levodopa 300mg	18.2%		2.3%			
				levodopa 150mg	16.3%		3.3%			
				placebo	13.3%		3.3%			
TEMPO study (2005) [16]	371	6 months	6 months	rasagiline						
				placebo						
TEMPO study (2009) [17]	177		5.5 years	rasagiline			6.1 years	not significant		
				placebo			6.0 years			
Sydney study (1994)[18]	149	3 years	5 years	levodopa	41%				11%	
				bromocriptine	37%				15%	
Sydney study (2005) [19]	52		15 years	levodopa	5.8 years	not significant	4.4 years	<0.01	13.1 years	not significant
				bromocriptine	6.6 years		6.9 years		11.6 years	
PDRG-UK trial (2008) [20]	782	3 months	14 years	levodopa	50%	not significant	58%	not significant	5.86	
				bromocriptine	56%		56%		6.17	
056 study (2000) [21]	268	6 months	5 years	levodopa			45%	<0.001		
				ropinirole IR			20%			
056 study (2007) [22]	80		10 years	levodopa	48%	not significant	7.0 years, 72.8%	<0.002		
				ropinirole IR	25%		8.6 years, 52.4%			
CALM-PD study (2007) [23]	301	10 weeks	1 year	levodopa				not significant		
				pramipexole IR						
STRIDE-PD study (2010) [24]	747	2.6 years	4 years	levodopa	1.5 years 50.8%	not significant	1.5 years 33.1%	not significant		
				levodopa+COMT-I	1.4 years 45.6%		1.4 years 38.6%			

levodopa was about 100 mg higher in the camptocormia group than in the non-camptocormia group [28].

Sleep attack while driving was related to a daily equivalent dose of levodopa [29]; patients on DA alone, or on combination therapy, had a significantly higher risk of sleep attacks than did patients on levodopa monotherapy [30]. From our study, however, this was not related to cumulative dose.

Hallucinations were more frequent among patients with early PD treated with DA compared to those who received placebo or levodopa [31], although a larger cumulative dose of DA was not a risk factor in our study. The amount of senile plaque and neurofibrillary tangles was higher in the brains of patients in the long-term antimuscarnic drug treatment group than of patients in the short-term treatment group [32]. Moreover, severe impairment in frontal lobe function was observed in the patients receiving anticholinergics [33]. However, in our study, trihexyphenidyl had no dose-dependent effects on psychosis or mental states.

Respiratory infection is a leading cause of death in patients with PD [34]. Patients with late-onset PD and male sex were at risk for developing pneumonia.

Study limitations

Our study did not examine disease progression or acceleration, and because it is a retrospective study, we could not exclude a number of relevant effects. We treated the patients with consideration of the known risks; patients who had been taking levodopa or had drug phobia, with hesitation to start or increase their dose of levodopa or other parkinsonian drugs, were treated with a smaller amount and cumulative dose of levodopa and other drugs. We cannot describe what degree of dose was not increased in the lower dose group. We did not include patients who died early. The patients were not randomized to treatment, and the variable duration to the start of the medication could reflect attempts to treat the appearance of symptoms. Hence, it is difficult to claim that different durations to the start of drug-use were causative risk factors for the prevalence of drug-related effects. Moreover, certain treatment outcomes differed from those of previously reported controlled prospective studies.

In conclusion, we investigated the cumulative dose of anti-parkinsonian drugs and various symptoms and complications in a large cohort of patients with PD. Larger cumulative dose of anti-parkinsonian drugs was not a risk factor for the examined symptoms of PD, and there was no relationship between the cumulative dose of anti-parkinsonian drugs and the prevalence of symptoms.

ACKNOWLEDGEMENTS

We thank the nurses and office workers, Department of Neurology, Juntendo University School of Medicine for their assistance reviewing charts.

Disclosures

A. Yoritaka, Y. Shimo, M. Takanashi, J. Fukae, T. Hatano, T.

Nakahara, N. Miyamoto, and T. Urabe report no disclosures. N. Hattori is a consultant for Boehringer Ingelheim, FP Pharmaceutical Company, Ohtsuka Pharmaceutical Company, Kyowa Hakko Kirin Pharmaceutical Company, GlaxoSmithKline, Novartis, Abbot, Hisamitsu, and Schering-Plough. He received personal compensation for attending advisory board meetings.

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Cite this article

Yoritaka A, Shimo Y, Takanashi M, Fukae J, Hatano T, et al. (2014) Motor and Non-Motor Symptoms of 1453 Patients with Parkinson 's Disease: Any Relationship with the Cumulative Doses of Anti-Parkinsonian Medications? J Neurol Disord Stroke 2(2): 1042.