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Calcium channel blockers and β -blockers in relation to Parkinson's disease

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Abstract

We investigated the risk of PD associated with calcium channel blockers (CCBs) and β -blockers in a population-based case-control study of 206 men and women between ages 35 and 89 with a new diagnosis of idiopathic PD between 1992 and 2002, and 383 controls without PD or other neurodegenerative disorders who were frequency matched on age, sex, duration of GHC enrollment and clinic. The adjusted odds ratio associated with ever use was 0.85 (95% confidence interval [CI]: 0.43, 1.66) for CCBs, and 1.20 (95% CI: 0.71, 2.03) for β -blockers. We observed no association with PD risk for either class of medication in terms of duration, dose, number of prescriptions or pattern of use. The weakness of these associations and the absence of additional influence of dose or duration of use argue against any causal interpretation.

Keywords

Parkinson's disease; Calcium Channel Blockers; β -blockers; Epidemiology; Case-Control

1. Introduction

Significantly decreased risks of Parkinson's disease (PD) associated with hypertension and blood pressure medication have been observed in several epidemiologic studies [1–2]. Because specific classes of medications were not identified in these studies, we investigated two common classes of anti-hypertensive medications, calcium channel blockers (CCBs) and β -blockers, that may potentially affect the risk of PD through different mechanisms. The possibility that CCBs may inhibit the Ca^{2+} -dependent process of apoptosis was first suggested in the cancer literature [3–6]. Based on this anti-apoptotic model, CCBs were subsequently hypothesized to be neuroprotective in PD and other conditions in which apoptosis contributes substantially to cell death [7]. In neuronal cell culture, nimodipine significantly inhibited β -

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amyloid apoptotic neuronal injury [8]. In animal models of PD, nimodipine also prevented neurotoxicity induced by 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP) in non-human primates [9] and in mice [10]. Based primarily on experimental studies and mechanistic considerations, we hypothesize that CCBs are associated with a decreased risk of PD.

β -blockers compete for available receptor sites, effectively reducing the neurotransmission of norepinephrine in the brain. Disturbances in the norepinephrine system may play an important role in the pathogenesis of PD by affecting both the onset and progression of damage to the dopamine nigrostriatal tract [11]. Specifically, loss of norepinephrine may enhance neurotoxic damage from environmental toxins to nigrostriatal dopaminergic neurons. Injections of MPTP into the brains of adult mice resulted in significant loss of dopaminergic cells in the substantia nigra only on the side of the brain where lesions were induced in the locus coeruleus, the primary source of norepinephrine [12]. In humans, loss of norepinephrine neurons in the locus coeruleus has been documented in patients with PD [13–14]. These findings support the hypothesis that the norepinephrine system may play a role in protecting the integrity of dopaminergic substantia nigral neurons [12]. Because β -blockers reduce the neurotransmission of norepinephrine, we hypothesize that β -blockers are associated with an increased risk of PD. To our knowledge, the current study is the first to examine the PD risk associated with CCBs and β -blockers. We assessed associations of PD with these anti-hypertensive medications using an automated pharmacy database in a population based case-control study of idiopathic PD.

2. Methods

We conducted the study among enrollees of Group Health Cooperative (GHC), a health maintenance organization in the Seattle area, who participated in a population-based case-control study of idiopathic PD. The methods have been described elsewhere [15]. Briefly, newly diagnosed idiopathic PD cases between 35 and 89 years of age were identified from GHC neurology and general medical clinics between 1992 and 2002. Medical charts of cases were reviewed by study neurologists (PDS, GMF, and WTL) to verify the presence of idiopathic PD based on the presence of at least two of the four cardinal signs: bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment. Cases were excluded if they had used antipsychotics, methyl dopa, reserpine or metoclopramide during the 12 months preceding symptom onset; had evidence of multiple cerebrovascular events prior to symptom onset as determined clinically or by brain imaging techniques; or had evidence of another cause of parkinsonism.

Controls were GHC enrollees without PD or other neurodegenerative disorders and were frequency matched to cases by age, sex, clinic, and duration of GHC enrollment. Medical charts of controls were reviewed to confirm the absence of neurodegenerative diseases at time of interview. From the interview, we obtained information on demographic factors, smoking history and medication conditions that are indications for or are associated with anti-hypertensive drug use, such as high blood pressure, heart disease and stroke. The study was approved by the Human Subjects committees at the University of Washington and the GHC Center for Health Studies. All participants provided written informed consent.

Information on use of CCBs and β -blockers was obtained from the GHC pharmacy database and without knowledge of case or control status. A computerized record has been created for every drug dispensed since March 1977, and includes information on drug type, therapeutic class, drug strength, drug form, date dispensed, quantity dispensed and dosing instructions (e.g., quantity of pills the subject was instructed to take). Prescriptions filled outside of the GHC's network of pharmacies, however, are not included in the computerized database. We assessed use of CCBs (e.g., verapamil, diltiazem, nifedipine, felodipine, amlodipine, nicardipine, bepridil) and β blockers (e.g., atenolol, propranolol, nadolol, metoprolol, labetalol,

carvedilol) up to 5 years before the interview date. We restricted our definition of users for each class of medication to those who filled at least two prescriptions. We characterized exposures to CCBs and β -blockers separately in terms of ever use (yes/no) and total number of prescriptions. In addition, we calculated cumulative duration of use, cumulative standard doses (defined below), average standard daily dose, and patterns of use.

To estimate the cumulative duration of use, we calculated the days of use by dividing the quantity of pills dispensed by the dosing instructions and summed the days of use. Dosing instructions were missing for 37.2% of 7,090 prescriptions of CCBs and 36.2% of 3,195 prescriptions for β -blockers. We imputed duration of use for prescriptions with missing dosing instructions by carrying the dosing information from the last observation with non-missing data forward for the same person on the same drug with the same pill strength. If dosing instructions were still missing, we applied the following set of rules sequentially: (1) carrying information from a subsequent observation with non-missing dosing instructions backward for the same person, drug and pill strength; (2) applying the mean value of the recommended daily maintenance dose range indicated in the GHC Formulary or in Drug Facts and Comparisons [16] publication if the drug was off-formulary. The doses obtained by referencing the GHC Drug Formulary or Drug Facts and Comparisons were verified using the recommended daily maintenance dose from Micromedex [17]. These imputation rules were applied without knowledge of case or control status. The proportion of cases and controls requiring imputation were similar for CCBs (5.8% and 4.5%, respectively, $p=0.47$) and for β -blockers (9.6% and 8.4%, respectively, $p=0.69$).

To obtain cumulative standard doses, we divided the total dose dispensed for each prescription by the minimum dose of the “usual” or “maintenance” range for hypertension as recommended in the GHC formulary, and summed the standard doses within each class of medication. We calculated the average daily standard dose by dividing cumulative standard doses by the cumulative duration of use. We also assessed continuity of use for a subset of subjects who were continuously enrolled in GHC for at least 10 years. To account for the possibility of occasionally missed doses that may not necessarily reflect overall sporadic use, continuity of CCB or β -blocker use was assessed assuming 70% compliance with dosing instructions. We defined continuous pattern of use as prescriptions dispensed continuously for at least 6 consecutive months. Otherwise, the pattern of use was considered intermittent.

In univariate analyses, we used χ^2 tests for categorical variables and analysis of variance for continuous variables. Medication use variables were categorized into three levels in which “no use” was the reference group. The remaining two categories were created by using the median values among users in the control group as cutoffs. To assess associations of PD with CCBs and β -blockers, we estimated odds ratios (ORs) and 95% confidence intervals (CI) for each class of medication using unconditional logistic regression, adjusting for age, sex, smoking, duration of GHC enrollment, and clinic. We evaluated possible confounding factors in multivariate models. CCBs and β -blockers were each considered as potential confounders for the other. To address the possibility that the use of these medications may have occurred while cases had subclinical PD, prescriptions dispensed within 5 years before the interview were excluded. For β -blockers, we also restricted one analysis to two lipophilic drugs (e.g., propranolol, metoprolol) that readily cross the blood-brain barrier. Analyses were performed using Stata version 7.0 (Stata Corp, College Station, Tex). Two-tailed tests with $P < 0.05$ were used to determine statistical significance.

3. Results

Medication data were available for 206 cases and 383 controls. Cases and controls did not differ with respect to age, sex, education, race, length of GHC enrollment, and self-reported

history of medical conditions including high blood pressure, stroke, and heart disease. Smoking was inversely associated with PD [15] and a smaller proportion of cases had a history of diabetes relative to controls, as reported previously (Table 1) [18].

Verapamil and diltiazem were most commonly dispensed, accounting for 34.5%, and 32.2% of the 7,090 prescriptions of CCBs that were dispensed to study participants. A similar proportion of cases and controls were dispensed prescriptions of CCBs (21.5% and 21.2%, respectively; $p=0.7$). Among controls, increasing length of CCB use was associated with male sex, greater duration of enrollment, smoking, increasing age, white race, use of β -blockers, and self-reported history of diabetes, heart disease, and high blood pressure (data not shown). Relative to nonusers, those who ever used CCBs had PD risk of 0.85 (95% CI 0.43, 1.66), after adjusting for age, sex, clinic, duration of enrollment, smoking, and use of β -blockers (Table 2). We observed no clear association between risk of PD with any aspect of CCB use including cumulative duration of use, cumulative standard doses, average daily standard doses, or total number of prescriptions dispensed. Among those who were continuously enrolled in GHC for at least 10 years prior to the interview, the likelihood of PD among continuous users was 0.54 (95% CI 0.15, 1.92) relative to nonusers. We observed no association with intermittent use (OR=0.92; 95% CI 0.43, 1.99). Adjusting for heart disease, stroke and high blood pressure did not change these estimates (Table 2).

A total of 3,195 prescriptions of β -blockers were dispensed to study participants. Atenolol accounted for 55.2% of total dispensed prescriptions, propranolol, 25.5%, and nadolol, 11.5%. A similar proportion of cases and controls used β -blockers (14.9% versus 16.4%, respectively, $p=0.6$). Among controls, increasing length of β -blocker use was associated with greater age, more years of enrollment, heart disease, high blood pressure and use of CCBs. We observed no association between ever use of β -blockers and risk of PD (OR=1.2; 95% CI: 0.71, 2.03) after adjusting for age, sex, smoking, duration of enrollment, clinic and heart disease. High blood pressure, stroke and CCBs did not influence the risk estimates. Among those continuously enrolled in GHC for at least 10 continuous years, intermittent and continuous use of β -blocker was not related to PD risk (Table 3). When analyses were restricted to propranolol and metoprolol, risk associated with either of these β -blockers was somewhat greater (OR=1.47; 95% CI: 0.80, 2.69) than when all β -blockers were included; this estimate, however, was well within the limits of chance.

4. Discussion

We did not observe any clear association between PD risk and CCBs, either for ever use or in terms of length, dose, number of dispensed prescriptions or pattern of use. Except for ever use and pattern of use for which risk estimates were decreased, the trend in the risk estimates for increasing dose of CCBs were in the opposite direction from what we had hypothesized. We also did not observe any clear relation between PD risk and β -blockers. Among those exposed to β -blockers, estimates of association were greater for those who used less β -blockers or used them for a shorter amount of time relative to users with greater or longer exposure to β -blockers. Given the unexpected pattern of risk estimates across increasing exposure categories to β -blockers, the observation that these estimates of association were stronger when analyses were restricted to propranolol and metoprolol, and the fact that propranolol is used to treat tremors, the observed increased risk only among those who used a lesser amount of β -blockers or used β -blockers for a shorter amount of time is largely influenced by prescriptions of propranolol used to treat tremors among cases with pre-clinical PD, rather than reflecting a true etiologic effect.

In humans, some case reports suggest a possible positive correlation between extrapyramidal symptoms or parkinsonism and use of CCBs, including flunarizine, cinnarizine, verapamil and

diltiazem [11,19] By contrast, several epidemiologic studies have reported decreased PD risk associated with hypertension and blood pressure medication [1–2]. Paganini-Hill et al. conducted a nested case-control study within a longitudinal cohort study of 13,979 residents of a retirement community in southern California, in which 395 PD cases identified from death certificates, hospital discharge diagnoses and follow-up questionnaire, and 2,320 controls were matched on sex, birth date and vital status. They observed a significantly decreased risk of PD with blood pressure medication (OR=0.63, 95% CI 0.48–0.80), which persisted in a multivariate analysis [1]. The discrepancies in the findings of this study and our study are likely to reflect differences in the methods used to identify PD cases, the timing of exposure to medications relative to case identification, and dissimilar definitions of exposure. In particular, the observed protective effect in the southern California study may reflect treatment changes after disease diagnosis or survivor bias stemming from a combination of ascertainment of current users of blood pressure medication and inclusion of prevalent PD cases and cases identified through death certificates. Our case group was restricted to newly diagnosed PD cases. In addition, medication use in the previously published study was broadly defined, whereas we used the computerized pharmacy database to identify and separately analyze specific classes of blood pressure medication.

The results of our study are not generalizable to ethnic or racial populations that are not well-represented in our population, including African-, Asian Americans, or people of Hispanic descent. Furthermore, our results could reflect differences in dispensing patterns among cases and controls, as well as incomplete ascertainment of drug exposures. Co-payments and changing policies on prescription drug coverage may have influenced study participants to fill their prescriptions outside GHC pharmacies. However, studies among GHC enrollees indicate that roughly 95% of members over age 65 filled all or almost all (90% or more) of their prescription medicines at a GHC pharmacy. One study examining the completeness of the GHC pharmacy database found that among a sample of 2389 GHC enrollees making a visit for back pain, headache, or joint pain in 1989–1990, 97% of prescriptions for propranolol and 94% of prescriptions for atenolol were always filled at GHC pharmacies [20]. Any misclassification of exposure due to incomplete ascertainment is not expected to differ between cases and controls.

The strengths of our study include its population-based design, use of incident cases of PD, and the availability of a computerized pharmacy database to assess detailed exposure to prescription medications, which should eliminate recall bias and provide more objective medication data than self-report. We excluded all prescriptions within 5 years before the interview date to avoid including medication exposure that occurred during the subclinical phase of PD. Medications have not been studied extensively as risk (or protective) factors for PD. To our knowledge, the current study is the first to examine CCBs and β -blockers in relation to PD. We did not observe any increased risk of PD with β -blockers, and our findings do not support the hypothesis of a neuroprotective effect of CCBs with PD risk.

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Table 1

Characteristics of PD Cases and Controls

Characteristics at Interview ^a	Cases (n=206)	Controls (n=383)
Age, mean (SD), y	69.2 (9.0)	69.4 (8.6)
Male, No. (%)	121 (58.7)	239 (62.4)
Length of GHC Enrollment, mean (SD), y	15.2 (6.5)	17.4 (6.6)
Education, $\geq$ High School, No. (%)	165 (80.1)	295 (77.0)
Non-Hispanic Caucasian, No. (%)	195 (94.7)	354 (92.4)
Smoking, No. (%) ^b		
Nonsmoker	113 (54.9)	154 (40.2)
0–19 pack-years	45 (21.8)	91 (23.8)
20–39 pack-years	26 (12.6)	77 (20.1)
40+ pack-years	22 (10.7)	61 (15.9)
High Blood Pressure, No. (%)	76 (37.1)	140 (37.1)
Heart Disease, No. (%)	57 (28.1)	111 (29.8)
Stroke, No. (%)	12 (6.1)	22 (5.9)
Diabetes No. (%) ^c	11 (5.4)	48 (12.8)

^aData were missing on duration of GHC enrollment for 1 case, 3 controls; on high blood pressure for 1 case, 6 controls; on heart disease for 3 cases, 10 controls; on stroke for 9 cases, 7 controls; on diabetes for 4 cases, 7 controls.

^b
p<0.01

^c
p<0.05

Table 2
Association of Incident Parkinson's Disease with Use of Calcium Channel Blockers

Exposure to Calcium Channel Blockers ^a	No. (%)		OR (95% CI) ^b
	Cases (n=191)	Controls (n=365)	
Ever Use			
No	169 (88.5)	324 (88.8)	1.0 (Ref)
Yes	22 (11.5)	41 (11.2)	0.85 (0.43–1.66)
Cumulative Duration of Use			
No Use	169 (88.5)	324 (88.8)	1.0 (Ref)
< 2.5 years	12 (6.3)	28 (7.7)	0.71 (0.31–1.62)
≥ 2.5 years	10 (5.3)	13 (3.6)	1.11 (0.43–2.88)
Cumulative Standard Doses			
No use	169 (88.5)	324 (88.8)	1.0 (Ref)
< 886	11 (5.8)	28 (7.7)	0.64 (0.29–1.42)
≥ 886	11 (5.8)	13 (3.6)	1.39 (0.56–3.44)
Average Daily Standard Doses			
No Use	169 (88.5)	324 (88.8)	1.0 (Ref)
< 1	7 (3.7)	18 (4.9)	0.59 (0.25–1.37)
≥ 1	15 (7.8)	23 (6.3)	1.44 (0.56–3.68)
Total Number of Prescriptions			
None	169 (88.5)	324 (88.8)	1.0 (Ref)
< 18	10 (5.2)	28 (7.7)	0.48 (0.17–1.39)
≥ 18	12 (6.3)	13 (3.6)	1.18 (0.54–2.59)
Pattern of Use ^c			
No Use	144 (88.3)	298 (88.2)	1.0 (Ref)
Intermittent	15 (9.2)	27 (8.0)	0.92 (0.43–1.98)
Continuous (for at least 6 months)	4 (2.5)	13 (3.9)	0.54 (0.15–1.92)

^aExcluding prescriptions within 5 years of interview

^bOdds ratio (OR) and 95% confidence intervals (CI) adjusted for age, sex, smoking, duration of enrollment, clinic, and use of β-blockers

^cRestricted to subjects continuously enrolled in GHC for at least 10 years.

Table 3
Association of Incident Parkinson's Disease with Use of β -blockers

Exposure to β -blockers ^a	No. (%)		OR (95% CI) ^b
	Cases (n=165)	Controls (n=321)	
Ever Use			
No	131 (79.4)	262 (81.6)	1.0 (Ref)
Yes	34 (20.6)	59 (18.4)	1.20 (0.71–2.03)
Cumulative Duration of Use			
No Use	131 (79.4)	262 (81.6)	1.0 (Ref)
< 3 years	20 (12.1)	34 (10.6)	1.23 (0.65–2.30)
$\geq$ 3 years	14 (8.5)	25 (7.8)	1.16 (0.54–2.52)
Cumulative Standard Doses			
No use	131 (79.4)	262 (81.6)	1.0 (Ref)
< 4300	15 (9.1)	23 (7.2)	1.38 (0.65–2.84)
$\geq$ 4300	19 (11.5)	36 (11.2)	1.07 (0.55–2.11)
Average Daily Standard Doses			
No Use	131 (79.4)	262 (81.6)	1.0 (Ref)
< 4	20 (12.1)	31 (9.7)	1.39 (0.72–2.66)
$\geq$ 4	14 (8.5)	28 (8.7)	0.99 (0.47–2.09)
Total Number of Prescriptions			
None	131 (79.4)	262 (81.6)	1.0 (Ref)
< 20	20 (12.1)	29 (9.0)	1.37 (0.72–2.62)
$\geq$ 20	14 (8.5)	30 (9.3)	1.00 (0.48–2.11)
Pattern of Use ^c			
No Use	96 (78.1)	205 (79.5)	1.0 (Ref)
Intermittent Use	7 (5.7)	17 (6.6)	0.92 (0.35–2.41)
Continuous (for at least 6 months)	20 (16.3)	36 (13.9)	1.17 (0.58–2.33)

^aExcluding prescriptions within 5 years of interview

^bOdds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, smoking, duration of enrollment, clinic, and heart disease

^cRestricted to subjects continuously enrolled in GHC for at least 10 years.

Table 4
Association of Incident Parkinson's Disease with Use of Propranolol or Metoprolol

Exposure to Propranolol or Metoprolol ^a	No. (%)		OR (95% CI) ^b
	Cases (n=165)	Controls (n=321)	
Ever Use			
No	140 (84.8)	284 (88.5)	1.0 (Ref)
Yes	25 (15.2)	37 (11.5)	1.47(0.80–2.69)
Cumulative Length of Use			
No Use	140 (84.8)	284 (88.5)	1.0 (Ref)
< 9 months	13 (7.9)	14 (4.4)	2.15 (0.94–4.94)
≥ 9 months	12 (7.3)	23 (7.2)	1.05 (0.47–2.35)
Cumulative Standard Doses			
No use	140 (84.8)	284 (88.5)	1.0 (Ref)
< 885	12 (7.3)	15 (4.7)	1.77 (0.77–4.07)
≥ 885	13 (7.9)	22 (6.9)	1.25 (0.56–2.78)
Average Daily Standard Doses			
No Use	140 (84.8)	284 (88.5)	1.0 (Ref)
< 4	13 (7.9)	17 (5.3)	1.72 (0.76–3.90)
≥ 4	12 (7.3)	20 (6.2)	1.26 (0.55–2.86)
Total Number of Prescriptions			
None	140 (84.8)	284 (88.5)	1.0 (Ref)
< 10	13 (7.9)	14 (4.4)	2.16 (0.94–4.94)
≥ 10	12 (7.3)	23 (7.2)	1.04 (0.46–2.34)

^aExcluding prescriptions within 5 years of interview

^bOdds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, smoking, duration of enrollment, clinic, and heart disease