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L-Type Calcium Channel blockers and Parkinson's Disease in Denmark

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Abstract

Objective—Investigate L-type calcium channel blockers of the dihydropyridine class for association with Parkinson's disease because these drugs traverse the blood brain barrier, are potentially neuroprotective, and have previously been evaluated for impact on PD risk.

Methods—We identified 1,931 patients with a first time diagnosis for PD between 2001 and 2006 as reported in the Danish national hospital/outpatient database and density matched them by birth year and sex to 9,651 controls from the population register. Index date for cases and their corresponding controls was advanced to date of first recorded prescription for anti-Parkinson drugs, if prior to first PD diagnosis in the hospital records. Prescriptions were determined from the national pharmacy database. In our primary analyses, we excluded all calcium channel blockers prescriptions 2-years before index date/PD diagnosis.

Results—Employing logistic regression analysis adjusting for age, sex, diagnosis of chronic pulmonary obstructive disorder, and Charlson co-morbidity score we found that subjects prescribed centrally acting calcium channel blockers (excludes amlodipine) between 1995 and two years prior to the index date were less likely to develop Parkinson's disease (Odds Ratio 0.73; 95% Confidence Interval 0.54-0.97); this 27% risk reduction did not differ with length or intensity of use. Risk estimates were close to null for the peripherally acting drug amlodipine and for other antihypertensive medications.

Interpretation—Our data suggest a potential neuroprotective role for centrally acting L-type calcium channel blockers of the dihydropyridine class in PD that should be further investigated in studies that can distinguish between types of L-Type channel blockers.

Introduction

The neurodegenerative movement disorder Parkinson's disease (PD) is well known for its progressive loss of dopamine (DA) producing brain cells. While pathological manifestations have been observed throughout the human nervous system,[1] the selective degeneration of substantia nigra pars compacta (SNc) DA neurons is still considered a key feature of PD. Unlike most neurons in the brain, adult DA neurons are L-type calcium (Ca^{2+}) channel-

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dependent autonomous pacemakers[2] that, in the absence of synaptic input, generate rhythmic action potentials. It has been suggested that reliance on Ca^{2+} channels might create a special DA neuron susceptibility to cellular aging. As discussed in recent reviews,[3,4] cells in which Ca^{2+} channels drive pacemaking may generally experience higher levels of basal oxidative stress due to ATP demands for intra-cellular calcium handling. But pacemaking may come at an especially high metabolic cost for DA neurons using $Ca_v1.3$ Ca^{2+} channels that open at relatively hyperpolarized potentials (as compared to the more common $Ca_v1.2$ channels). This particular neuronal environment may compromise biologic mechanisms linked to PD, including mitochondrial function and protein processing,[5,6] contributing to the pathogenic processes of dopaminergic neurodegeneration.

Since cardiac and smooth muscles also depend on L-type Ca^{2+} channels, substances that block or modify their action have been used to primarily treat hypertension as well as angina and arrhythmia in humans for decades. While the two most commonly prescribed drugs, verapamil (phenylalkylamine) and diltiazem (benzothiazepine), are potent vasodilators they non-selectively block Ca^{2+} channels and at therapeutic levels their concentrations in the brain and activity upon Ca^{2+} channels of DA neurons are unknown. Medications of the dihydropyridine class more selectively act on L-type channels (both $Ca_v1.2$ and $Ca_v1.3$) by allosterically modulating the gating of the channel and exhibit brain bioavailability.[7] To date only three studies have examined calcium channel blocker (CCB) use in humans in connection with occurrence of PD.[8,9,10] A Spanish cohort study[10] and a US case control study[8] did not observed any association between CCB use and PD, but neither study was able to distinguish between classes of channel blockers. The much larger UK General Practice Research Database study[9] suggested a protective association for current but not past use of dihydropyridine CCBs but did not distinguish between drugs more or less capable of traversing the blood brain barrier and binding to receptors in the brain.[11]

To our knowledge, we are presenting the first study evaluating specific L-type dihydropyridine CCBs with good brain bioavailability in a large population-based case control study conducted in the Danish population utilizing the nationwide prescription database and National Hospital Register.

Subjects and Methods

The study protocol was approved by the Danish Data Protection Agency and the UCLA Office for Protection of Research Subjects.

Study Population

Denmark's National Health Service provides free equal access to healthcare for the entire population. Each health service-related event is recorded in national databases, including the Hospital Register[12] and the Registry of Medical Products Statistic (the national prescription database[13]) both of which can be linked to each other and the Central Population Registry using a unique personal identification number assigned to all Danish citizens at birth or when awarded citizenship.

We conducted a population-based case control study using a record linkage approach within this registry system. PD cases were ascertained from the Hospital Register that has recorded all hospitalizations since 1977 and all clinic visits - including outpatient clinics - since 1995. Using density sampling and the Population Registry, roughly five age- and sex-matched controls were selected per case. For 1986 - 2006, we identified 82,140 subjects (13,695 cases with a primary diagnosis of PD in the Hospital Register and 68,445 controls) who (1) had a valid personal identification number (2) were over age 35 at the time of diagnosis and (3) had not emigrated from Denmark. We further restricted the study sample to all cases

(and their matched controls) registered for the first time with a primary diagnosis of Parkinson's disease (*International Classification of Diseases, 10th revision*, code G20) between Jan 2001 and Dec 2006. To identify the earliest possible date of PD diagnosis, we set as the index date the first hospital or outpatient record that ever mentioned PD or the first prescription of PD medication (anatomical therapeutic chemical (ATC) code N04B)[14], whichever was earlier. If the index date fell into the period before 2001, the case and the case's matched controls were excluded resulting in 13,123 total subjects (2,188 cases and 10,935 controls). We further excluded PD patients who had never received a PD drug prescription (257 cases and their matched controls), leaving 1,931 PD cases and 9,651 controls. Controls were assigned the same index date as their matched case. In sensitivity analyses, we further excluded PD cases (and their matched controls) and controls diagnosed with any type of dementia (both Alzheimer type and unspecified) or cerebrovascular disease before the index date (305 cases, 2,282 controls).

Assessment of prescription drug use

Since Jan 1995, the national prescription database has received data on dispensed prescriptions from all pharmacies in Denmark.[13] This database includes the individual's personal identification number, drug type by ATC code, and dispensing date. For each study subject, we identified other anti-hypertensive and CCB prescription data prior to index date: dihydropyridines acting centrally (excludes amlodipine) (C08CA02-06, CA08-09, CA13); amlodipine (C08CA01); and the non-dihydropyridines verapamil (C08DA01) and diltiazem (C08DB01). Due to differences in lipophilic properties, we distinguished between L-type channel blockers in the dihydropyridine class that cross the blood brain barrier (felodipine, isradipine, nicardipine, nifedipine, nimodipine, nitrendipine, lacidipine, lercandipine) and the one dihydropyridine class CCB thought to not cross as readily (amlodipine). We also examined prescriptions for other anti-hypertensive drugs: angiotensin (AT) II antagonists (ATC-group C09C and C09DA), beta blockers (ATC-group C07A), and hydrophilic (ATC-group C09AA01-03) and lipophilic (ATC-group C09AA04-AA07; AA09, AA15) angiotensin-converting enzyme (ACE) inhibitors, respectively.

Anti-hypertensive and CCB ever use was defined as filling 2 or more prescriptions during the relevant periods of time prior to the index date and nonusers otherwise. For users, we also created a variable capturing duration of use and intensity of use according to the World Health Organization's[14] defined daily doses (DDDs) per package, e.g. average intensity per day equaled the sum of all package DDDs between the date of second CCB prescription and the last prescription plus 60 days, divided by the number of days in this period.

Statistical Analysis

We used unconditional logistic regression to calculate odds ratios (OR) for CCB use and 95% confidence intervals (CI) while adjusting for age (continuous), sex, co-morbidities registered before the index date (using the Charlson index[15]), and chronic obstructive pulmonary disease (COPD) diagnosis identified in the Hospital Register (ICD codes J42-J44 and 490.00, 491.00, 491.01, 491.03) as a proxy for heavy smoking. In some analyses, we also adjusted for the use of other anti-hypertensive drugs. The Danish population is primarily Caucasian so we did not adjust for race/ethnicity. Analyses for duration and intensity of CCB use were based on tertiles defined by the control population's distribution.

For our primary analyses, we advanced the index date (lagged) by 2 years; e.g. a subject was considered exposed to a medication only if he/she had received two or more prescriptions two years prior to the onset of PD as defined above. Lagging use is preferable primarily because of the presumed preclinical period of PD, and because our case identification

methods may have ascertained some prevalent PD cases. We also lagged the Charlson index and COPD by 5 years to capture the general health status of subjects prior to the index date.

Results

Cases and controls, having been matched on birth year and sex, were on average 72.2 years of age at the index date; as expected, we identified more male than female cases. Five years prior to the index date, the general health of cases and controls was similar according to the Charlson index (Table 1). At the unlagged index date, two or more prescriptions for amlodipine had been received by 10.3% of all study subjects, while prescriptions for all other dihydropyridines were rarer (3.5%).

Our logistic regression analyses consistently estimated a 26-30% reduction in PD risk in models (Table 2) employing a 2-year lag for ever prescription use of centrally acting L-type dihydropyridine Ca^{2+} channel blockers (excludes amlodipine); we did not observe dose-response patterns in our effect estimates according to duration or intensity of use (Supplementary Table S1). Results were similar in the unlagged analysis (ever/never OR 0.74, 95% CI 0.57-0.97), when lagging by 5 years (OR 0.68, 0.49-0.97) or excluding subjects with cerebrovascular disease or dementia diagnoses prior to the index date (OR 0.79, 0.57-1.10).

By contrast, amlodipine prescription drug use was not associated with risk of PD (Table 2) under similar models, and no associations with PD risk were seen for the non-dihydropyridine CCBs verapamil and diltiazem or the AT II antagonists (Table 3). Ever use of beta-blockers was associated with a slightly increased risk of PD when employing a 2-year lag (OR 1.29, 1.13-1.48); this association was attenuated at a 5-year lag (OR 1.16, 0.99-1.37). We also observed a slight difference in the risk estimates between lipophilic (OR 0.90, 0.68-1.20) and hydrophilic (OR 1.16, 0.96-1.41) ACE inhibitor use. Results were similar when stratified by age of onset of PD (<=60, >60 years) or gender.

Discussion

We identified all cases with a primary diagnosis of PD in Denmark between 2001-2006 in the national Hospital Registry and relied on an ongoing national prescription database created in 1995 to adjust the index date to first prescription drug use for PD and to determine CCB and anti-hypertension drug use among cases and matched population controls. We found a 26-30% decrease in PD risk for subjects prescribed L-type calcium channel blockers of the centrally acting dihydropyridine class (excludes amlodipine) during the period between 1995 and two years prior to the index date. On the other hand, the more commonly prescribed, peripherally acting dihydropyridine amlodipine and several common non-dihydropyridine CCBs were not associated with PD risk in our study population.

Since CCBs are primarily used in the treatment of hypertension, we also investigated associations between PD and other common anti-hypertensive drugs. Animal and cell studies have suggested that AT II antagonists and ACE inhibitors may be neuroprotective due to antioxidant properties.[16-17] We did not expect these drugs to affect Ca^{2+} channels (and by extension protect against PD) since AT II antagonists and ACE inhibitors act on the renin-angiotensin system, therefore our observed lack of association between AT II and PD in our study population is not unexpected. In contrast, the novel finding that direction of the associations for ACE inhibitor prescriptions depended on whether they were lipophilic (decreased risk) or hydrophilic (increased risk) warrants further investigation. Our observed increased risk of PD in subjects prescribed beta-blockers is likely explained by the use of these drugs in treating essential tremor, and thus the observed positive association may

result from insidious symptoms during the prediagnostic phase of PD.[18] This explanation is supported by the attenuated association in our 5-year lagged analyses and the fact that beta blockers act on the norepinephrine system, not on Ca^{2+} channels.

To date, three other epidemiologic studies have reported on CCB prescription use and PD. A study of 191 idiopathic PD cases and 383 controls identified between 1992 and 2002 in the Puget Sound health care system[8] suggested a negative association between PD and ever use of any type of CCB, but was hampered by small sample size (OR 0.85, 0.43-1.66). This US-based study lagged exposure by 5 years but evaluated all CCBs together: two-thirds of which were the non-dihydropyridines verapamil and diltiazem, drugs with no known action on DA neuron L-type Ca^{2+} channels at therapeutic levels. The much larger UK General Practice Research Database[9] case-control study compared current (within 90 days of PD diagnosis), longer term (≥30 prescriptions) users to non-users among 3,637 incident PD cases diagnosed between 1994 and 2005 and an equal number of matched controls. Their negative association with PD for current, long term use of dihydropyridine (OR 0.78, 0.62-0.99) as well as non-dihydropyridine type (OR 0.76, 0.52-1.10) CCBs are likely confounded by pre-clinical disease since PD patients are known to develop neurogenic orthostatic hypotension,[19] which would lead to a discontinuation of anti-hypertensive medications.[20] We attempted to minimize such bias by identifying the earliest possible PD diagnosis date and lagging our exposure 2 and 5 years from that index date. The most recent Spanish cohort study[10] followed 5,278 subjects for 3 years and evaluated CCB use at baseline for associations with prevalent (n=81) and incident (n=30) PD, separately. While utilizing prospectively collected longitudinal data, the small number of exposed PD cases (N=11) basically rendered this study uninformative. Furthermore, unlike our study in the Danish population, this study did not distinguish between different types of CCBs.

Our study was hampered by the relatively short average follow-up time for CCB prescriptions which may explain the lack of an association for our measures of duration and intensity. Due to the recent establishment of the prescription drug database (est. 1995), we could only examine relatively short-term anti-hypertensive use with adequate statistical power. However, we likely captured nearly all regular, continuing, and compliant CCB users in Denmark as Ca^{2+} channel blockers are only available with a prescription and our data were derived from the nationwide prescription database. The universal coverage of most health care expenses in Denmark makes it less likely that drug prescriptions or PD diagnoses were influenced by factors determining access to care. Given the record-based nature of our dataset, we attempted to adjust for smoking using COPD diagnosis as a proxy for heavy smoking; most likely we controlled for smoking no more than partially.

Our findings might be affected by disease misclassification since PD cases were identified from hospital and clinic records and may have included some patients with non-idiopathic Parkinsonism which would have been largely excluded by a movement disorder specialist evaluation. Sensitivity analyses in which we excluded PD cases and controls with prior diagnoses of dementia and cerebrovascular diseases before the index date suggested this bias to be minimal. Controls were selected at random from a population registry and did not have to volunteer information for our study, thus, we have avoided bias due to selective non-participation. Because we identified PD cases from hospital and clinic records, we might have constructed a case set of less healthy PD patients compared to broader PD population of Denmark. The higher Charlson index among our study's PD patients compared to controls 2 years prior to and at the index date (data not shown) might support the possibility for such a selection bias; but, given the long pre-clinical course of PD, these values may simply reflect the declining health of PD patients prior to diagnosis. Interestingly, differences in general health status were not evident 5 years prior to PD diagnosis/index date (p-value =0.42, Table 1).

The L-type dihydropyridine calcium channel blockers nifedipine, nimodipine, and isradipine have been observed at 6 to 9 times the concentration of amlodipine in the brains of intravenously treated mice;[11] the dihydropyridine ring of amlodipine is in a positively charged state at physiological pH whereas the other dihydropyridines are non-charged; [21,22] and amlodipine is hydrophylic[23] while others such as nimodepine are strongly lipophilic.[24] All of which provides biological support for the observed differences between dihydropyridine CCBs (excludes amlodipine) and amlodipine. Non-amlodipine dihydropyridine CBBs traverse the blood brain barrier more efficiently than amlodipine, which is likely to need a transporter due to its positive charge. Although verapamil and diltiazem CCBs traverse the blood brain barrier, neither is known to bind to the $Ca_v1.3$ L-type channels that dominate SNc DA neurons;[3] this is consistent with the absence of an association with PD for these frequently prescribed anti-hypertensives. A recent murine study has shown that bathing SNc DA neurons in or subcutaneous administration of the L-type calcium channel blocker isradipine or deletion of the *Cacna1d* gene that encodes the $Ca_v1.3$ subunit returns autonomous pacemaking to a latent ionic mechanism using Na^+/HCN-channels.[25] Other members of the dihydropyridine class, like nimodipine, may act similarly as suggested by studies in non-human primates.[7,26] The transition of pacemaking activity from Na^+/HCN channels to $Ca_v1.3$ Ca^{2+} channels as cells age suggests that elevations in cytosolic Ca^{2+} might contribute to aging-related oxidative, mitochondrial, and endoplasmic reticulum stress. Supporting this claim, Chan et al.[25] showed that isradipine treatment protected against SNc DA neuron loss and motor deficits in mice undergoing low dose repeated administration of the neurotoxin MPTP. Furthermore, nimodipine and nitrendipine treatment provided neuroprotection from cytosolic DA-induced cell death in SNc neurons.[27] Our findings, in combination with these observations in model systems, support the hypothesis that centrally-acting CCBs targeting $Ca_v1.3$ Ca^{2+} channels of DA neurons might decrease risk of PD, possibly through decreasing general cellular stress thereby attenuating the impact of environmental or genetic insults in aging DA neurons. Given that hypotension is a common feature and manifests preclinically in many PD patients, further investigations and a more complete understanding of their biological and potential neuroprotective role are essential before considering these anti-hypertensive medications for therapeutic uses in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of Danish Study Population, 2001-2006 (total N=11,582)

	Cases (n=1,931)	Controls (n=9,651)
Age, mean (std)	72.2 (10.5)	72.2 (10.5)
Sex (% male)	1,121 (58.1)	5,603 (58.1)
Birth Year (n, %)		
1900-1909	3 (0.2)	15 (0.2)
1910-1919	254 (13.2)	1269 (13.2)
1920-1929	737 (38.2)	3684 (38.2)
1930-1939	568 (29.4)	2840 (29.4)
1940-1949	266 (13.8)	1329 (13.8)
1950-1959	73 (3.8)	364 (3.8)
1960-1969	30 (1.5)	150 (1.5)
Charlson index[1] (n, %)		
0	1456 (75.4)	7399 (76.7)
1	251 (13.0)	1220 (12.7)
≥2	224 (11.6)	1032 (10.6)
COPD diagnosis[1] (n, %)		
No	1912 (98.9)	9500 (97.9)
Yes	21 (1.1)	203 (2.1)
Dihydropyridine Medications[2] (n, %)		
Amlodipine	161(8.3)	766(7.9)
All other dihydropyridines	55 (2.8)	368(3.8)
Median Length of Use[3] (years)	2.7	3.5

[1] Five year lag from index date (e.g. earliest date of diagnosis of PD or PD medication use for cases).

[2] Medication use is defined as two or more prescriptions between 1995 and 2 years prior (2 year lag) to index date (e.g. earliest date of diagnosis of PD or PD medication use for cases). Note: 8% of users (1% of the total study population) received more than 1 type of CCB.

[3] Median length of prescription drug use for any dihydropyridine starting after a second CCB prescription until index date.

Table 2

Associations between L-type dihydropyridine calcium channel blocker prescriptions (2 year lag) and Parkinson's disease (N=11,582)

	Cases (n=1,931) N (%)	Controls (n=9,651) N (%)	Model 1 OR[1] (95% CI)	Model 2 OR[2] (95% CI)	Model 3 OR[3] (95% CI)
Ever use, dihydropyridine CCBs excludes amlodipine					
No	1876 (97.2)	9283(96.2)	ref	ref	ref
Yes	55 (2.8)	368(3.8)	0.74 (0.55-0.99)	0.73 (0.54-0.97)	0.70 (0.52-0.94)
Ever use, amlodipine					
No	1770(91.7)	8885(92.1)		ref	
Yes	161(8.3)	766(7.9)		1.04 (0.87-1.25)	

[1] Adjusted for age, sex

[2] Adjusted for age, sex, COPD (5 year lag), Charlson index (5 year lag)

[3] Adjusted for age, sex, COPD (5 year lag), Charlson index (5 year lag), other anti-hypertensive drugs (non-dihydropyridine CCBs, amlodipine, beta blockers, ACE inhibitors, and AT II antagonists- 5 year lag)

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Table 3

Associations between other anti-hypertensive prescription use (2 year lag) and Parkinson disease (N=11,582)

	Cases (n=1,931) N (%)	Controls (n=9,651) N (%)	OR[1] (95% CI)
Non-dihydropyridine CCBs [2]			
No	1797 (93.1)	9087 (94.2)	ref
Yes	134 (6.9)	564 (5.8)	1.14 (0.93-1.39)
Beta-blockers			
No	1579 (81.8)	8236 (85.3)	ref
Yes	352 (18.2)	1415 (14.7)	1.29 (1.13-1.48)
ACE inhibitors			
No	1743 (90.3)	8828 (91.5)	ref
Yes	188 (9.7)	823 (8.5)	1.11 (0.93-1.32)
AT II antagonists			
No	1835 (95.0)	9162 (94.9)	ref
Yes	96 (5.0)	489 (5.1)	0.94 (0.74-1.19)

[1] Adjusted for age, sex, COPD (5 year lag), Charlson index (5 year lag), non-dihydropyridine CCBs (2 year lag), amlodipine (2 year lag), beta blockers (2 year lag), ACE inhibitors (2 year lag), and AT II antagonists (2 year lag)

[2] Non-dihydropyridine CCBs include phenylalkylamine (verapamil) and benzothiazepine (diltiazem) derivatives