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Calcium channel blocker use and risk of Parkinson's disease

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Abstract

Purpose—To investigate whether the use of calcium channel blockers (CCBs) was associated with a reduced risk of Parkinson's disease (PD) in two large prospective cohorts.

Methods—Prospective cohort study among participants in two ongoing studies – the Nurses' Health Study (NHS) and Health Professionals' Follow-Up Study (HPFS). Cox proportional hazards models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) to assess the association between use of CCBs and risk of PD adjusting for potential confounders.

We identified 514 incident cases of PD during follow-up of individuals enrolled in the NHS and HPFS. No association between baseline use of CCBs (RR=1.18, 95% CI: 0.73, 1.92), frequency of use or duration of use of CCBs and PD risk was observed ($P>0.2$ for all).

Conclusions—These findings do not support a role for CCBs in providing neuroprotection against development of PD.

Introduction

Experimental evidence supports a potential role for calcium in dopaminergic cell death¹ associated with Parkinson's disease (PD). Neurons of the substantia nigra differ from other neurons in that they maintain autonomous electrical activity and therefore are exposed to increased calcium ion influx, which may increase SNc susceptibility to perturbations of calcium homeostasis². Recently, Chan and colleagues³ found that a L-type calcium channel blocker (CCB), isradipine, reduced dopaminergic cell damage from 6-OHDA injection or MPTP administration in mice and suggested that the use of calcium channel blockers CCBs may confer protection against PD. This hypothesis has been examined in two case-control studies, one of which found a significantly decreased risk of PD associated with CCB use⁴, while the other found no significant association with PD risk⁵. We therefore further examined this hypothesis by taking advantage of two large prospective cohorts of men and women with 514 incident PD cases from sixteen years of follow-up.

Methods

Study Population

The study population includes 121,700 female participants in the Nurses' Health Study (NHS) aged 30-55 and 51,529 male participants in the Health Professionals Follow-up Study (HPFS) aged 40-75 who returned detailed information on disease and lifestyle factors in 1976 and 1986, respectively. Risk factor information and disease occurrence are updated via biennial questionnaires. Follow-up for the current investigation began in 1986 for men and 1988 for women, the first years in which use of calcium channel blockers (CCBs) was reported, and continued until the date of death, date of PD or end of follow-up (Jan 31, 2002 for men and June 31, 2002 for women). Participants with prevalent PD and stroke were excluded, resulting in a study population of 120,530 women and 50,825 men included in the analyses.

Case ascertainment

A question regarding history of PD was first asked in 1988 in men and 1994 in women and then updated biennially and ascertainment in these cohorts has been previously described⁶. Briefly, for individuals who self-reported a new diagnosis of PD, we requested permission to contact the treating physician to obtain medical records or a questionnaire detailing the certainty of the physician's diagnosis. A case was considered confirmed if it was determined to be a definite or probable case by the treating physician (84.6% neurologist, 9.7% internist) or if blinded medical record review by a movement disorder specialist (5.7%) found a final PD diagnosis by a neurologist or 2 of 3 cardinal features (bradykinesia, resting tremor, rigidity) in the absence of evidence suggesting an alternative diagnosis.

Calcium channel blockers

Questions on specific anti-hypertensive medications were asked beginning in 1986 for men and 1988 for women. Participants were asked whether they were currently using CCBs or other anti-hypertensive medications (beta-blockers, thiazide diuretics and other anti-hypertensives) at baseline. Thereafter, participants were asked biennially whether they regularly used these medications in the previous 2 years.

Statistical analysis

Cox proportional hazards models were used to obtain relative risks (RRs) and 95% confidence intervals (CIs) to assess the association between a history of calcium channel blocker use and risk of PD adjusting for age and smoking (quintiles of pack-years). Two separate analyses were conducted, one based on ever use of CCBs as reported at baseline, and one updating the information on use of CCBs every two years. In the first analyses, individuals were classified as non-users of antihypertensive drugs (reference), users of CCBs (with or without other anti-hypertensive medications), or users of other anti-hypertensive medication without CCBs. In the second analyses, to examine whether duration and regularity of use of CCBs were associated with PD risk, individuals were considered as: i) never users (if they did not report use at baseline or in any of the follow-up questionnaires); ii) past users (if they reported use prior to, but not including the questionnaire in which they reported a diagnosis of PD), or iii) current users with cumulative duration of use < 4 years or ≥ 4 years (the median CCB use in the cohort). Because we hypothesized that CCB use specifically, not overall anti-hypertensive medication use, may be protective for PD, in all analyses, a history of CCB use was considered regardless of use of other anti-hypertensive medications. Notably, the proportion of CCB users reporting concurrent use of other anti-hypertensive medications was small (15%). Further analyses were conducted considering regularity of CCBs use during the follow-up; in these analyses

participants were categorized as never users, regular users (those who reported use in at least two consecutive biennial questionnaires) or irregular users (those who reported use at baseline or during follow-up, but not consecutively reported on biennial questionnaires).

Resulting log RRs from men and women were combined using inverse variance weights and fixed effects models as tests of heterogeneity were non-significant at the $\alpha=0.05$ level.

Results

We identified 514 incident cases of PD (324 men, 190 women) during follow-up. The average age at diagnosis was 68 years for men and 67 years for women. Baseline characteristics of the study population according to use of anti-hypertensives are shown in Table 1. As expected, individuals using anti-hypertensive medications reported higher BMI, and history of hypertension. Overall, risk of PD was not associated with self-reported history of CCB use amongst all participants or in gender specific analyses.

The risk of PD was not significantly increased among individuals who reported CCBs use at baseline or during the follow-up (Tables 2 & 3). In analyses considering baseline use of CCBs and risk of PD, we also calculated effect estimates considering all non-CCB users as the referent (non-users of anti-hypertensives and users of other anti-hypertensives) and results were virtually identical. Results were similar upon further adjustment for reported history of hypertension and other potential PD risk factors including BMI, physical activity, caffeine, alcohol and total energy intake.

Discussion

Perturbations in calcium homeostasis have been seen in *in vitro* experiments using cells with mitochondria from PD patients⁷ and after administration of MPTP⁸. Additionally, differences in calcium levels have been observed amongst PD patients compared to healthy individuals⁹. Calcium is involved in mitochondrial functioning and activates key proteins in apoptotic pathways, and both of these mechanisms have been postulated as causal in relation to PD¹⁰, suggesting that blocking of calcium pathways may confer neuroprotection.

However, our results do not support a beneficial role of CCBs in PD at doses habitually used to treat hypertension. These findings are consistent with the recent population based case-control study of HMO enrollees where medication use was obtained from pharmacy database⁵. In that study, ever use of CCB was associated with 15% lower risk of PD, though this did not approach statistical significance and further, no association was observed with dosage, total number of prescriptions or pattern of use of CCB. Conversely, our results are somewhat in contrast with the main findings in the General Practice Research Database, in which current use of CCBs was associated with a 20% decreased risk of PD⁴. There are several differences between these studies. The Ton et al. study and our own are considerably smaller than the GPRD study which included over 800 exposed cases and reported a higher prevalence of CCB use. In addition, a significant inverse association between CCB use and PD in the GPRD was only found among current users of CCBs, which included individuals with prescriptions within 90 prior to the date of PD diagnosis. Given the insidious onset of PD and the fact that there are often years between the report of a first symptom and diagnosis, the association between exposure and outcome should be assessed well before disease onset, preferably years¹¹. Differences in the age of PD cases between the studies may also be relevant. A lower risk of PD among CCB users in the GPRD was only observed for PD diagnoses after the age of 80 years, which were very few in our study that comprises an overall younger population. Further, in the GPRD the association was stronger and

significant only among women; because CCB use was relatively rare among women in our cohort, we had little power to determine gender-specific effects.

Some non-differential misclassification of exposure is expected in our study as medication use was self-reported and would likely bias towards the null, thus attenuating any effect estimate. However, given the participants are all health professionals, the potential bias from this source is likely modest, and given our point estimate is greater than 1, would be unlikely our finding is consistent with a protective effect of CCBs. Additionally, we did not have detailed information on medication use so could not evaluate potential differences in types of calcium channel blockers. As in all observational studies, there is a potential for confounding which may have obscured a true association. However, we adjusted for several potential confounders including factors consistently associated with PD risk, and these had little impact on effect estimates, suggesting it is unlikely that confounding explains these results. We cannot generalize our findings to other populations, particularly of different socioeconomic status. The HPFS and NHS cohorts are comprised of health professionals and, therefore, are likely to have a higher degree of educational attainment. However, it seems unlikely that a potential biological relationship between CCB use and PD would vary based on this fact. Also of note, our results are based on a small number of exposed cases and, therefore, the power to detect moderate odds ratios is modest. However, our estimates should be unbiased, even if underpowered, and although the confidence intervals include protective effects, the point estimates do not suggest a protective effect.

Although the results of our study do not support a beneficial effect of CCB in the doses commonly used in clinical practice, further studies in larger populations and including more detailed information on CCBs use are warranted to provide a more definitive conclusion.

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Table 1

Age adjusted baseline characteristics of study population according to use of anti-hypertensive medication use

	No anti-hypertensive medication use	Calcium channel blocker use*	Other anti-hypertensive medication use
WOMEN	n=82,901	n=2695	n=16,967
Age (yrs), mean (std. dev)	54.0 (7.2)	58.0 (6.3)	56.9 (6.8)
Current smokers (%)	20.4	18.1	17.3
Past smokers (%)	36.0	40.5	38.6
Caffeine intake (mg/day)	292	246	249
Alcohol consumption (g/day)	6.2	5.6	6.3
Physical activity (MET)	14.5	12.5	12.7
BMI (kg/m ²)	25.1	27.3	27.6
Energy Intake (kcal/day)	1773	1735	1751
History of hypertension (%)	16.8	71.1	76.7
MEN	n=41,491	n=1131	n=8204
Age (yrs), mean (std. dev)	53.5 (9.6)	62.7 (8.2)	59.9 (8.9)
Current smokers (%)	10.2	13.3	10.1
Past smokers (%)	42.7	53.4	47.1
Caffeine intake (mg/day)	244.3	188.8	222
Alcohol consumption (g/day)	11.6	11.1	13.4
Physical activity (MET)	21.6	17.3	17.1
BMI (kg/m ²)	25.3	26.2	26.5
Energy Intake (kcal/day)	1998	1856	1934
History of hypertension (%)	9.4	53.1	85.1

* - Use of calcium channel blockers, with or without concurrent use of another anti-hypertensive medication

Table 2
Risk of Parkinson's disease associated with baseline calcium channel blocker use

	# cases	Person-years	RR (95% CI) [†]	p-value	Multivariable-adjusted RR (95% CI) [‡]	p-value
All participants						
Non-users	403	1740784	REF		REF	
CCB users	18	47258	1.21 (0.75, 1.95)	0.43	1.18 (0.73, 1.92)	0.50
Users of other anti-hypertensives	93	298628	1.12 (0.89, 1.41)	0.34	1.10 (0.84, 1.46)	0.49
WOMEN						
Non-users	141	1089329	REF		REF	
CCB users	5	33600	0.85 (0.35, 2.09)	0.73	0.81 (0.32, 2.03)	0.65
Users of other anti-hypertensives	44	220947	1.17 (0.83, 1.65)	0.37	1.15 (0.75, 1.77)	0.53
MEN						
Non-users	262	651455	REF		REF	
CCB users	13	13658	1.39 (0.79, 2.43)	0.25	1.32 (0.75, 2.33)	0.34
Users of other anti-hypertensives	49	77681	1.08 (0.79, 1.47)	0.63	1.07 (0.75, 1.54)	0.71

Non-users did not report use of any anti-hypertensive medication at baseline (calcium channel blocker or other).

[†] Adjusted for age and pack-years of smoking

[‡] Additional adjustment for history of hypertension, caffeine intake, alcohol consumption, BMI, physical activity and total calorie intake

Table 3

Risk of Parkinson's disease associated with duration and regularity of calcium-channel blocker use

	# cases	Person-years	RR (95% CI)	p-value
Never users of CCBs	444	1910678	REF	
CCB users				
Past	28	56344	1.23 (0.83, 1.81)	0.31
Current, <4 yrs	21	65515	1.06 (0.68, 1.65)	0.80
Current, ≥4 yrs	21	54141	1.05 (0.67, 1.65)	0.83
Never users of CCBs	444	1910678	REF	
Use of CCBs				
Irregular	37	96151	1.17 (0.83, 1.64)	0.37
Regular, ≥4yrs	33	79849	1.03 (0.73, 1.46)	0.85

The referent (never users) are those who did not report use of CCBs on any questionnaire cycle prior to censoring. This includes individuals who did not use any anti-hypertensives and those who used anti-hypertensives other than calcium channel blockers.

Adjusted for age and pack-years of smoking