Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging

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Abstract

Background: Concern has been raised about the potential for adverse cognitive effects associated with the use of calcium-channel blockers (CCBs) in older people. This study was undertaken to examine prospectively the association between the use of these and other antihypertensive drugs and cognitive function.

Methods: The authors examined data from the Canadian Study of Health and Aging (CSHA), a population-based, prospective 5-year investigation of the epidemiology of dementia and other health problems in Canadians 65 years of age and older. The risk of cognitive decline, as indicated by a decline in performance on the Modified Mini-Mental State (3MS) examination over the 5-year period, was assessed in relation to the use of antihypertensive and diuretic drugs by 205 subjects with a history of hypertension and no evidence of dementia at baseline.

Results: The proportion of subjects whose cognitive performance declined over the study period was significantly higher in the group using CCBs than in the group using other antihypertensive agents (75% v. 59%). The adjusted odds ratio (OR) for a significant decline in cognitive performance (defined as a decrease in 3MS score of 10 points or more) was 2.28 (95% confidence interval [CI] 1.12–4.66) for subjects using CCBs. The adjusted ORs (and 95% CIs) for cognitive decline in subjects using selected antihypertensive agents or diuretics relative to those exposed to β-blockers were as follows: angiotensin-converting-enzyme inhibitor, OR 1.36 (95% CI 0.41–4.55); diuretic or other antihypertensive drug, OR 1.45 (95% CI 0.51–4.14); dihydropyridine CCB (nifedipine), OR 1.94 (95% CI 0.52–7.27) and non-dihydropyridine CCB (diltiazem or verapamil), OR 3.72 (95% CI 1.22–11.36).

Interpretation: Older people taking CCBs were significantly more likely than those using other agents to experience cognitive decline. These findings are consistent with the results of previous cross-sectional research and emphasize the need for further trials to examine the associations between CCB use, blood pressure and cognitive impairment in elderly patients.

There is increasing controversy regarding the long-term cognitive effects of calcium-channel blockers (CCBs) on elderly people. Heckbert and associates,[1] in a cross-sectional study of 1268 older hypertensive participants in the US Cardiovascular Health Study, demonstrated that subjects using CCBs had more hyperintensity of the cerebral white matter on MRI (which may have reflected chronic ischemia) and worse cognitive performance than β-blocker users. These adverse associations were especially pronounced for people using dihydropyridine CCBs. An earlier randomized, double-blind, crossover trial demonstrated that hypertensive subjects treated with nifedipine had worse scores on tests of learning and memory than users of atenolol.[2] Conversely, in the Syst-Eur trial, active treatment with primarily another CCB, nitrendipine, was associated with a lower incidence of dementia.[3]

Cerebrovascular disease can lead to a variety of lesions that may be associated with vascular dementia, including multi-infarct dementia, strategic single-infarct dementia, small-vessel disease with dementia, hypoperfusion and hemorrhagic de-

Evidence

Études

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mentia.[4] Hypertension in midlife appears to be an important risk factor for the development of cognitive impairment in later life.[5–7] Midlife hypertension may lead to arteriolosclerosis of small cerebral blood vessels. This in turn may contribute to impaired cerebral autoregulation and result in increased vulnerability to ischemia during periods of reduced cerebral blood flow,[8,9] possibly induced by antihypertensive agents such as CCBs.

Given the high prevalence of hypertension among older people[10,11] and the widespread use of CCBs,[12] further evaluation of the cognitive effects of these medications is warranted. The potential public health impact of this issue is considerable, given that it may be possible to modify a person's antihypertensive regimen. Previous research in this area has been limited by the use of cross-sectional designs or relatively small samples. Our primary objective was to address these limitations by examining, in a prospective manner, the association between exposure to CCBs and other antihypertensive and diuretic agents and subsequent cognitive performance in a cohort of elderly patients.

Methods

Sample

Our analyses are based on data from the Canadian Study of Health and Aging (CSHA). The CSHA was a population-based, prospective investigation of the epidemiology of dementia and other health issues within a representative sample of Canadians 65 years of age and older. The study involved 18 centres grouped into 5 geographic regions (British Columbia, the Prairie provinces, Ontario, Quebec and the Atlantic provinces). The total sample consisted of 10 263 people, 9008 from the community and 1255 residing in institutions, who were initially interviewed between February 1991 and May 1992. This initial cohort is identified here as CSHA-1.

All subjects living in the community first underwent a standardized interview that included a cognitive screening test, the Modified Mini-Mental State (3MS) examination.[13] Subjects scoring below 78 on the 3MS examination (which has a maximum score of 100), a random sample of those with a score of 78 or higher, and subjects who could not be screened with this test were invited to undergo a clinical examination (n = 1165). In addition, all subjects living in institutions underwent the 3MS and clinical examinations. The clinical examination was multidisciplinary; it included a medical history, a physical examination and neuropsychologic testing for those with 3MS scores of 50 or higher. Neuroimaging was not performed. A consensus conference was held to review all available information and to classify each person as cognitively normal, cognitively impaired but not demented, or demented (on the basis of the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* [third edition, revised][14]). If the person was classified as demented, a specific diagnosis as to the likely cause was made on the basis of criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) for Alzheimer's disease[15] and *International Classification of Diseases* (10th revision) criteria for vascular dementia.[16] A more comprehensive description of the study design and methodology has been published elsewhere.[17]

For the second cycle of the study (CSHA-2), the original cohort was contacted again in 1996/97, approximately 5 years after the baseline examination. The follow-up assessment was equivalent to that performed at baseline.

The present analyses were restricted to subjects who underwent the clinical examination, who were identified at baseline as not having dementia, who were using one or more antihypertensive or diuretic medications and who had a history of hypertension.

Measures

During the baseline clinical examination, subjects were asked to report their current use of prescription and over-the-counter drugs. For subjects living in institutions, drug data were obtained from a review of health records. The drug data were coded according to the American Hospital Formulary System Pharmacologic/Therapeutic Classification Scheme (published by the American Society of Hospital Pharmacists). We classified subjects according to their use of the following drugs: CCBs, β-blockers, angiotensin-converting-enzyme (ACE) inhibitors, and thiazide diuretics or other antihypertensive agents. Subjects using loop diuretics (n = 28) were excluded, because they represented an arguably "sicker" subgroup with a relatively poorer prognosis (the primary indication for these drugs is edema associated with congestive heart failure, cirrhosis of the liver or renal disease).[18] We compared the risk estimates for subjects using a dihydropyridine CCB (nifedipine, n = 23) with those for subjects using non-dihydropyridine CCBs (diltiazem and verapamil, n = 45). Subjects using more than one agent were classified in a stepwise manner starting with CCB use. Subjects using any combination of a CCB and another antihypertensive agent were grouped with those using CCBs only. Next, those using any combination of a β-blocker and another drug (excluding CCBs) were grouped with those using β-blockers only. This process was repeated for users of ACE inhibitors.

The following covariates were examined: sex, age, history of stroke, history of diabetes, cardiac symptoms as recorded by the examining physician, smoking status, sitting systolic and diastolic blood pressure, and use of other drugs (digoxin, nitrate, ASA, non-ASA NSAIDs, anticoagulants, estrogen or vitamin E). Cardiac symptoms included chest pain, dyspnea, palpitations or edema (or any combination of these). Information on specific cardiovascular symptoms, diagnoses and procedures (e.g., palpitations, angina, myocardial infarction, arrhythmia, congestive heart failure, coronary artery bypass graft surgery or carotid endarterectomy) was collected during CSHA-2, and these variables were also examined, with adjustment for date of occurrence where possible. Current or past heavy smokers were identified from proxy responses to the question "Has he/she ever been a heavy smoker, say 20 or more cigarettes a day for a year or more?" CSHA-1 measures of self-rated health, activities of daily living, body mass index and creatinine levels were excluded from the analyses because of numerous missing values.

Global cognitive status was assessed with the 3MS examination, as previously described.[13] Possible scores on this examination range from 0 to 100, higher values representing better cognitive function. A binary outcome measure for cognitive decline was derived from the difference in subjects' 3MS scores over the 5-year period (1996 score minus 1991 score); a decrease of 10 points or more was coded as a decline. There is no agreement in the literature on the magnitude of change in the 3MS score that should be considered clinically significant. A recent study of participants in the Cardiovascular Health Study considered a 3MS decline of 5 points or more over 3 years to represent a clinically significant change.[19] We

chose a decline of 10 points or more because of the longer follow-up period and because this represented (approximately) the standard deviation for the sample. Supportive evidence for the relevance of this outcome was our finding of a significantly higher rate of admission to an institution among subjects who had a decline of 10 points or more (33.3%; 15 of 45 subjects) than among those with a less severe decline (10.7%; 14 of 131 subjects). Similarly, the rate of dementia in these 2 groups was 53.9% (35 of 65 subjects) and 5.0% (8 of 159 subjects) respectively. We examined the relation between use of a CCB or other antihypertensive drug and a diagnosis of dementia, the presence of vascular cognitive impairment (including vascular dementia, possible Alzheimer's disease with a vascular component and vascular cognitive impairment without dementia)[20] and admission to an institution at follow-up.

Analysis

Bivariate associations were examined by means of cross-tabulations, χ^2 tests of significance for categorical variables and *t*-tests for continuous variables.

Multivariate logistic regression techniques[21] were used to examine the independent effects of subjects' characteristics and use of antihypertensive agents and the relative importance of these variables to cognitive decline. Use of antihypertensive drugs was coded as a binary variable (CCB v. other agents), and dummy variables were used to compare subjects taking specific antihypertensive or diuretic drugs to the reference group of β-blocker users. Users of β-blockers were chosen as the reference group to provide a comparable approach to that used by Heckbert and associates[1] and because within our sample this group had the lowest prevalence of cognitive decline.

Results

A total of 509 subjects met our criteria for inclusion in these analyses. Of this group, 276 were lost to follow-up because of death (201 subjects), refusal to participate (24) or unavailability for some other reason (36), or because the 3MS score from either baseline or the second cycle was missing (15). Thus, data from 205 subjects were available for analysis.

Our analyses of all-cause mortality within the initial sample of 509 subjects showed a significantly higher risk of death for nifedipine users (but not for users of other antihypertensive or diuretic agents) than for β-blocker users after adjustment for potential confounders (hazard ratio of 1.82, 95% confidence interval [CI] 1.09–3.04).

For all drug groups (CCBs, β-blockers, ACE inhibitors, thiazide diuretics and other antihypertensive agents), the proportion of subjects receiving only one agent was greater than 50% (Table 1). The mean duration of use at baseline was 34.6 months for CCB users, 70.3 months for β-blocker users, 33.9 months for ACE inhibitor users and 75.1 months for users of diuretics or other antihypertensive drugs. About 61% of subjects who were using a CCB at baseline (in 1991) also reported CCB use in 1996/97 (46 of 76 subjects), and about 86% of those who were not using a CCB at baseline reported no CCB use in 1996/97 (114 of 132 subjects).

The rates of cardiac symptoms and nitrate use were significantly higher among subjects using CCBs than among users of other drugs, as was the proportion of subjects with a history of stroke (Table 2). Because of the small numbers of subjects, use of anticoagulants, estrogen and vitamin E were excluded from the remaining analyses.

Subjects using CCBs showed a greater mean decline in 3MS score from baseline and were significantly more likely than users of other antihypertensive drugs to exhibit poorer cognitive performance at follow-up (75% v. 59%). About 34% of CCB users (28 of 68 subjects) and 24% of users of other antihypertensive drugs (33 of 137 subjects) experienced a decrease in their 3MS score of 10 points or more. CCB users also had a greater risk of vascular cognitive impairment at follow-up, and the rate of admission to institution was higher (though nonsignificant) in this group.

Table 3 presents the unadjusted and adjusted odds ratios (ORs) for cognitive decline (defined as a decrease in the 3MS score of 10 points or more). Current or past heavy smoking was not significantly associated with cognitive decline at the bivariate level and was excluded from the final model because of missing values. After adjustment for selected covariates, subjects using CCBs exhibited a significantly greater risk for cognitive decline (OR 2.28). These findings were unchanged by the incorporation of CSHA-2 data on specific cardiovascular symptoms, diagnoses and

Table 1: Use of antihypertensive and diuretic drugs, alone and in combination, by 205 subjects in the Canadian Study of Health and Aging

Drug group	Total no. of subjects	No. (and %) of subjects receiving monotherapy	No. (and %) of subjects receiving combination therapy*		
			β-Blocker	ACE inhibitor	Thiazide diuretic
CCB	68	39 (57)	13 (19)	4 (6)	19 (28)
β-Blocker	37	21 (57)	– –	3 (8)	14 (38)
ACE inhibitor	34	23 (68)	– –	– –	11 (32)
Thiazide diuretic†	56	56 (100)	– –	– –	– –
Other‡	10	10 (100)	– –	– –	– –

Note: CCB = calcium-channel blocker, ACE = angiotensin-converting enzyme.
*Some patients were receiving more than 2 drugs in combination.
†Includes thiazides and related agents or thiazides in combination with potassium-sparing diuretics.
‡Other drugs were central α-blocker ($n = 6$), adrenergic neuron blocker ($n = 1$), α_1-adrenergic blocker ($n = 2$) and hydralazine ($n = 1$). Because of small numbers of subjects, this group was collapsed into the group of thiazide diuretic users for subsequent analyses.

procedures for subjects with cardiac symptoms at baseline. Age was positively associated with cognitive decline (OR 1.33 for 5-year increase), and there was a significant inverse association for nitrate use (OR 0.11). Subjects with a history of diabetes and those with relatively lower diastolic blood pressure exhibited a higher (though nonsignificant) risk of decline. The removal of nonsignificant variables from our model had no effect on the risk estimates.

The risk estimates for cognitive decline associated with specific antihypertensive agents compared with β-blockers are presented in Table 4. Relative to subjects using β-blockers, only those using non-dihydropyridine CCBs had a significantly greater risk for cognitive decline (OR 3.72), after adjustment for selected covariates.

Interpretation

This prospective investigation showed that older people who had a history of hypertension and who were taking CCBs were significantly more likely than subjects taking

Table 2: Demographic and health characteristics and antihypertensive drug use (1991 data) and measures of cognitive function (1991 and 1996 data)

Characteristic	Drug group; no. (and %) of subjects*		
	All drug groups *n = 205*	CCB *n = 68*	Other antihypertensive *n = 137*
Demographic			
Sex			
Women	144 (70)	49 (72)	95 (69)
Men	61 (30)	19 (28)	42 (31)
Mean age (and SD), yr	77.8 (5.7)	77.6 (5.0)	77.9 (6.1)
Health			
History of stroke	26 (13)	11 (17)	15 (11)
History of diabetes	20 (10)	8 (12)	12 (9)
Cardiac symptoms	59 (29)	31 (46)	28† (20)
Heavy smoker (ever)	50 (26)	19 (30)	31 (23)
Mean blood pressure (and SD), mm Hg			
Diastolic	81.2 (11.7)	80.3 (11.1)	81.7 (12.0)
Systolic	152.9 (23.1)	151.1 (22.4)	153.7 (23.5)
Digoxin use	20 (10)	7 (10)	13 (9)
Nitrate use	25 (12)	14 (21)	11‡ (8)
ASA use	59 (29)	22 (32)	37 (27)
Non-ASA NSAID use	41 (20)	13 (19)	28 (20)
Anticoagulant use	2 (1)	0 (0)	2 (1)
Estrogen use	4 (2)	1 (1)	3 (2)
Vitamin E use	7 (3)	1 (1)	6 (4)
Antihypertensive drug use			
CCB	68 (33)	–	–
β-Blocker	37 (18)	–	–
ACE inhibitor	34 (17)	–	–
Diuretic or other antihypertensive	66 (32)	–	–
Cognitive function			
3MS score, mean (and SD)			
In 1991	80.1 (10.9)	80.2 (10.2)	80.0 (11.3)
In 1996	73.9 (18.2)	72.0 (17.3)	74.9 (18.6)
Difference (1996–1991)	–6.1 (14.5)	–8.2 (14.7)	–5.1 (14.3)
Dementia (1996)§	38 (18)	11 (16)	27 (20)
Vascular cognitive impairment (1996)¶	36 (20)	15 (25)	21 (17)
Admission to an institution (1996)**	51 (17)	19 (20)	32 (16)

Note: SD = standard deviation, 3MS = Modified Mini-Mental State examination.
*Except where indicated otherwise.
†Statistically significant difference between CCB group and group using other antihypertensive drugs, $p < 0.001$.
‡Statistically significant difference between CCB group and group using other antihypertensive drugs, $p < 0.01$.
§$n = 67$ for CCBs and $n = 138$ for other antihypertensive drugs because more data were available in 1996. However, these data exclude clinical data from Newfoundland, because a legal interpretation of the province's advance directives legislation held it to be unacceptable for a proxy to give consent to participate in a research study on behalf of a person unable to give fully informed consent themselves.
¶Includes vascular dementia, possible Alzheimer's disease with vascular component and vascular cognitive impairment without dementia.
**$n = 97$ for CCBs and $n = 201$ for other antihypertensive drugs.

other antihypertensive agents or diuretics to experience cognitive decline during the 5-year follow-up period of the CSHA. This higher risk was unchanged after adjustment for several potential confounding factors and was evident for users of non-dihydropyridine CCBs only. The lack of a significant risk of cognitive decline among subjects using dihydropyridine CCBs may be related to the small sample numbers or to differential attrition rates (or both), in that we also found a significantly higher risk of death among nifedipine users (but not among users of diltiazem or verapamil) than among β-blocker users in the larger CSHA sample. These findings are consistent with the results of previous research on this topic[1] and with the results of 2 randomized trials, which illustrated no difference in cognitive function between subjects exposed to a thiazide and those receiving a β-blocker[22] or an ACE inhibitor.[23] We found no significant association between cognitive decline and use of ACE inhibitors, other antihypertensive drugs or diuretics relative to use of β-blockers.

A higher rate of vascular cognitive impairment (vascular dementia, possible Alzheimer's disease with a vascular component or vascular cognitive impairment without dementia) and a trend toward a greater likelihood of admission to an institution at follow-up were found among the subjects taking CCBs than among those taking other agents. Both of these associations may reflect underestimates, because some of the subjects who were lost to the analyses because of death may have had dementia, and, as noted above, users of dihydropyridine CCBs had a significantly higher risk of death than users of other antihypertensive agents.

Heckbert and associates[1] reported significantly lower mean 3MS scores for users of both CCBs and loop diuretics. Although we excluded users of loop diuretics from the present analyses, we also found a significantly higher risk of cognitive decline within this group (data not shown). It is possible that CCBs and loop diuretics pose a particular risk for some patients by increasing the likelihood of episodic decreases in blood pressure and cerebral blood flow. Other, as-yet-unexplored mechanisms may also be involved.

Age, nitrate use and, to a lesser extent, history of diabetes were also associated with cognitive decline. The relation of age to cognitive impairment is well known.[17,24,25] There is also evidence of an increased risk of cognitive impairment with diabetes.[5,26,27] The relevance of the significant inverse association observed for nitrate use is uncertain and warrants further exploration.

A particular strength of this investigation is that it is based on data from a 5-year prospective study. This allowed us to establish a temporal relation between use of antihypertensive drugs and cognitive decline. Most subjects taking a CCB at baseline had been doing so for a considerable length of time and also reported such use at follow-up. The present analyses included a larger sample of older hypertensive persons and a longer follow-up period than did a previous longitudinal investigation.[2] Because the CSHA was initiated to explore the epidemiology of dementia, many of the relevant risk factors for cognitive impairment were assessed and could be adjusted for in our analyses.

One concern with the interpretation of our findings is the potential for confounding by indication. We attempted to control for possible comorbid differences between users of CCBs and other agents with multivariate adjustment and by selecting β-blocker users as the reference group (CCBs and β-blockers are both indicated for treatment of hypertension or angina). However, the possibility remains that these drugs may have been preferentially prescribed for more severely ill patients or that their use may represent a proxy for some unmeasured variable predisposing to cognitive decline. Although only a general measure of cardiac symptoms was available at baseline, we attempted to address this limitation by incorporating CSHA-2 data on specific cardiovascular symptoms, diagnoses and procedures. The use of these more specific indicators of cardiovascular disease in our multivari-

Table 3: Unadjusted and adjusted odds ratios* (ORs) for cognitive decline† associated with use of antihypertensive drugs and demographic and health characteristics in the 205 subjects

Characteristic	Unadjusted OR (and 95% CI)	Adjusted OR (and 95% CI)
CCB use	1.61 (0.85–3.05)	2.28 (1.12–4.66)
Sex (female)	1.22 (0.62–2.42)	1.05 (0.49–2.24)
Age (increase of 5 yr)	1.29 (0.98–1.69)	1.33 (0.99–1.80)
History of stroke	1.45 (0.61–3.48)	1.34 (0.49–3.64)
History of diabetes	1.48 (0.56–3.93)	2.62 (0.85–8.09)
Cardiac symptoms‡	0.59 (0.29–1.22)	0.73 (0.31–1.71)
Digoxin use	0.88 (0.30–2.53)	1.18 (0.36–3.85)
Nitrate use	0.20 (0.05–0.89)	0.11 (0.02–0.61)
ASA use	1.25 (0.64–2.43)	1.35 (0.62–2.93)
Non-ASA NSAID use	0.83 (0.38–1.82)	0.82 (0.34–1.96)
Diastolic blood pressure (increase of 5 mm Hg)	0.90 (0.78–1.03)	0.88 (0.76–1.02)

Note: CI = confidence interval.
*Obtained from multivariate logistic regression model, adjusted for all variables listed in this table.
†Defined as a decrease in 3MS score of 10 points or more.
‡The incorporation of a history of specific cardiovascular symptoms or diagnoses and vascular procedures (e.g., palpitations, angina, myocardial infarction, arrhythmia, congestive heart failure or coronary artery bypass graft surgery) reported in 1996 for those reporting cardiac symptoms at baseline (in 1991), did not alter the findings for this model.

Table 4: Unadjusted and adjusted ORs* for cognitive decline† associated with use of selected antihypertensive drugs by the 205 subjects

Characteristic	Unadjusted OR (and 95% CI)	Adjusted OR (and 95% CI)
β-Blocker (reference group)	1.00	1.00
ACE inhibitor	1.54 (0.50–4.74)	1.36 (0.41–4.55)
Diuretic or other antihypertensive	1.49 (0.55–4.00)	1.45 (0.51–4.14)
Nifedipine	1.51 (0.44–5.24)	1.94 (0.52–7.27)
Diltiazem or verapamil	2.60 (0.94–7.22)	3.72 (1.22–11.36)

*Obtained from multivariate logistic regression model, adjusted for age, sex, use of other drugs, history of stroke or diabetes, cardiac symptoms and diastolic blood pressure.
†Defined as a decrease in 3MS score of 10 points or more.

ate analyses did not alter the significant association observed for CCB use. Although most subjects in our sample were not classified as demented, the sampling strategy and the age and baseline 3MS scores of the subjects (Table 2) indicate that this group was probably cognitively vulnerable.

The consistency of our findings with those reported by Heckbert and associates[1] underlines the need for further evaluation of the potential adverse cognitive effects of CCBs. The Vascular Dementia Project of the Syst-Eur trial showed that the incidence of dementia (primarily Alzheimer's disease) was lower among elderly patients with isolated systolic hypertension receiving active therapy with nitrendipine.[3] Unfortunately, this trial did *not* provide data on potential differential cognitive effects associated with various antihypertensive agents. Relative to the Syst-Eur sample, our subjects were older and had poorer cognitive performance and lower blood pressure levels at baseline. Also, we had a greater number of incident cases of dementia during follow-up (38 cases during 1025 patient-years in our study v. 22 cases during 4894 patient-years in the Syst-Eur study). The protective effect observed in the Syst-Eur trial may have been due to the lowering of blood pressure. However, no protective effect against dementia was found in the Systolic Hypertension in the Elderly Program (SHEP), which used a thiazide derivative, despite a reduction in blood pressure and a lower risk of stroke.[28] There is a need for large, prospective trials to examine the associations between treatment of hypertension, changes in blood pressure and cognitive function in the elderly.

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