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The Effect of Donepezil Treatment on Cardiovascular Mortality

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Abstract

The acetylcholinesterase inhibitor donepezil hydrochloride improves cognitive function in patients with Alzheimer's disease and vascular dementia. Given acetylcholine's important actions on the heart, we undertook a retrospective cohort investigation to assess whether donepezil usage affects cardiovascular mortality. In patients treated with donepezil, hazard ratios for total and cardiovascular mortality were 0.68 ($P = 0.045$, 95% confidence interval 0.46–0.99) and 0.54 ($P = 0.042$, 95% confidence interval 0.30–0.98), respectively. The apparent survival benefit in donepezil-treated patients should not be overinterpreted. Prospective clinical trials are warranted.

The acetylcholinesterase inhibitor donepezil hydrochloride improves cognitive function in patients with Alzheimer's disease and vascular dementia.^{1,2} However, this agent also increases the availability of acetylcholine in peripheral tissues, including the heart, where it augments vagal influences on sinus node and cardiac conduction systems. Both sinus node function and conduction deteriorate with age.³ Aging-associated changes in sinus node function may be related to calcium channel ($\text{Ca}_v1.2$) downregulation.⁴ A reduction in the levels of connexin-43 expression (which is essential for electrical cell-to-cell stimulation) has been implicated in aging-associated deterioration of the conduction system.⁵ Therefore, the elderly and very elderly are at particularly high risk for potentially life-threatening dysfunctions of the sinus node or conduction system. Augmented availability of acetylcholine in the heart through acetylcholinesterase inhibition could conceivably exacerbate the risk of bradycardia in this population. On the other hand, augmented acetylcholine could be beneficial, given the poor cardiovascular outcome in patients with diminished cardiac vagal activity.^{6,7} Indeed, acetylcholinesterase inhibition appears to

reduce overall mortality in patients with moderate to severe Alzheimer's disease⁸ and Parkinson's disease-related dementia.⁹ We conducted a retrospective cohort investigation to assess whether donepezil usage affects cardiovascular mortality in patients with Alzheimer's disease or vascular dementia.

RESULTS

We identified 1,004 patients with Alzheimer's disease and vascular dementia out of a total of 1,736 admissions. Donepezil was prescribed for 85 patients at the time of their discharge. Of those, 76 fulfilled all our inclusion and exclusion criteria. Of the 915 patients who did not receive donepezil, we randomly selected 80 patients matched for age, sex, and race to serve as the control group (Table 1). The majority of the patients enrolled had Alzheimer's disease. The main reasons for hospital admissions were respiratory symptoms (28%) in donepezil-treated patients and orthopedic (15%) and cardiac causes (15%) in untreated patients.

Over a mean follow-up period of 29 ± 17 months in donepezil-treated patients and 28 ± 25 months in untreated patients, we identified 115 fatal events. Of these, 88 were available in the medical records and were successfully matched to the Tennessee death-certificate database. In 27 patients, fatal events were determined solely from this database. Fatal cardiovascular events occurred in 36 donepezil-treated and 18 untreated patients ($P < 0.01$). Cox proportional hazard regression analysis showed that, relative to the untreated group, donepezil-treated patients had lower total mortality risk and also lower cardiovascular mortality risk (after adjusting for potential confounders such as vascular dementia, age, sex, and ethnicity) (Table 2). Additionally, Kaplan–Meier survival analysis showed better overall and cardiovascular survival in donepezil-treated patients in the first 3–4 years of follow-up (Figure 1). The intergroup difference disappeared after 4–5 years, probably because of the small number of surviving patients.

DISCUSSION

Given donepezil's mechanism of action and the high risk for sinus node dysfunction or cardiac conduction impairment in patients receiving the drug, we were concerned that there could be an increase in fatal cardiovascular events in donepezil-treated patients. Instead, our retrospective analysis showed better cardiovascular and overall survival in donepezil-treated patients. Our study has several important limitations and must be interpreted with caution. First, the numbers of patients, both donepezil-treated and untreated, were relatively low. Second, although both groups were carefully matched, a bias such as physicians' decisions on discharge prescriptions could not be eliminated because all the data were retrospectively collected from hospital discharge summaries. Finally, although recent clinical studies demonstrated that donepezil is well tolerated,² we have no information concerning medication compliance in our study. Despite these limitations, we believe that our analysis contains clinically relevant information that deserves to be addressed in prospective studies.

Theoretically, donepezil could affect the functioning of the sinus node and cardiac conduction systems through central nervous and peripheral mechanisms. Donepezil has previously been shown to raise brain acetylcholine availability.¹⁰ Central cholinergic stimulation could raise blood pressure through the release of vasopressin¹¹ and the activation of the sympathoadrenal system.¹² Baroreflex-mediated bradycardia could occur. More likely, acetylcholinesterase inhibition could induce bradycardia through actions on cardiac muscarinic receptors, as has been shown in rats¹¹ and in human subjects.¹³ However, whether or not donepezil raises heart rate variability, which is strongly influenced by vagal influences on the sinus node, is controversial.^{14,15} Previous studies suggested that

vagal heart rate control may be impaired in patients with Alzheimer's disease.^{16,17} It is possible that such impairment in vagal function could have decreased the likelihood of life-threatening bradycardia in the patients in our study.

Potentially favorable prognostic influences of donepezil may not be confined solely to improvement in cognitive function.^{18,19} For instance, tacrine, another cholinesterase inhibitor, did not alter life expectancy in spite of beneficial actions on cognitive and global function.²⁰ It is possible that augmented vagal function contributes to the survival benefit seen with donepezil. For example, chronic electrical stimulation of the vagus nerve improved long-term survival in rats with congestive heart failure after a large myocardial infarction.²¹ Recent studies suggest that acetylcholine from vagal stimulation protects cardiomyocytes from acute hypoxia and ischemia, in part through hypoxia-inducible factor-1 α .²² Moreover, the antiarrhythmia effect of vagal stimulation was accompanied by preservation of phosphorylated connexin-43 protein.²³ Cholinesterase inhibition reduced the levels of thrombomodulin and β -thromboglobulin, which are markers of endothelial and platelet activation, respectively.²⁴ Finally, donepezil might have a role in direct stimulation of acetylcholine synthesis in cardiomyocytes through mechanisms other than acetylcholinesterase inhibition.²⁵

In conclusion, our retrospective cohort study showed that donepezil was associated with reduced cardiovascular mortality in patients with Alzheimer's disease or vascular dementia. Given the limitations of our study, the apparent survival benefit in donepezil-treated patients should not be overinterpreted. However, our observations, as well as data from previous studies suggesting that improved survival is associated with acetylcholinesterase inhibition,^{8,26–28} should be scrutinized in mechanistic studies and in larger clinical trials. In particular, we suggest investigating in greater detail the action of donepezil on the cardiovascular system in patients with Alzheimer's disease or vascular dementia. Prospective studies for a duration of several years may be required to gauge the overall risks and benefits of donepezil treatment in this vulnerable population.

METHODS

The institutional review board of Vanderbilt University and the Tennessee Department of Health approved the study protocol.

Data source

We retrospectively obtained data from the Hospital Discharge Data System database of Tennessee, the Vanderbilt Hospital medical record database (StarPanel), and the Tennessee death-certificate database (Tennessee Department of Health Death Data System Manual 2004, Bureau of Health Informatics, Office of Health Statistics). To protect the privacy of the subjects, we removed all traceable, person-specific identifying information from the data set created by linking subjects across the three data sources. Each subject was assigned an anonymous, coded study number.

Patient selection

We included patients with Alzheimer's disease or vascular dementia admitted to Vanderbilt Hospital between 1 January 1997 and 31 December 2003. The clinical diagnosis of probable Alzheimer's disease or vascular dementia was determined by the attending physicians on the basis of the complete medical history, neurological examination, blood chemistry, and computed tomography of the brain. We excluded patients who had a follow-up period of <14 days. The patients had to be Tennessee residents because we relied on the state's death-certificate database. We identified donepezil-treated patients and compared their outcomes

with those of randomly selected patients, matched for age, sex, and ethnicity, who had not been treated with donepezil.

Patient characteristics and outcomes

Via the Vanderbilt Medical Center record database (StarPanel), we acquired information on patients' age, sex, ethnicity, residence, dementia diagnosis, chief complaint at admission, past medical history, prognosis, cardiovascular events, and fatal events. Dates and causes of death were identified from the Tennessee death-certificate database (Tennessee Department of Health Death Data System Manual 2004, Bureau of Health Informatics, Office of Health Statistics) up to 31 December 2005. Patients who survived up to the time of discharge from the hospital and whose names were not found in the death-certificate database up to the cutoff date were considered to be alive as of that date. We use the major code of the Tennessee death-certificate database for demographic description and analysis of data for patients who had fatal events. The causes of death were organized in subclasses as shown in Table 3. The primary end point was a fatal cardiovascular event. The secondary end point was occurrence of any fatal event. Cardiac events experienced by the patients, including acute coronary syndrome or decompensated heart failure at the time of admission to Vanderbilt Hospital, were investigated. Furthermore, any cardiovascular event for which patients were admitted to the Vanderbilt cardiac unit during the follow-up period was also investigated.

Statistical analysis

Demographic distributions and clinical characteristics were determined for subjects who were prescribed donepezil (DPZ⁺ group) and for those who were not (DPZ⁻ group). Data are presented as mean $\pm$ SD for continuous variables and as frequencies for categorical variables. Comparisons between the two groups were performed using Mann–Whitney *U*-tests. The Pearson χ^2 -test was used for categorical variables. Overall patient survival was analyzed using a Cox proportional hazards model to control for covariates. Cox proportional hazards regression models were applied to compare survival rates in the DPZ⁺ and DPZ⁻ patients at the time of discharge from the hospital. The models were adjusted for the effect of independent mortality risk factors including vascular dementia, age, sex, and race. Kaplan–Meier survival curves were constructed to assess the probability of survival free from all fatal events and cardiovascular fatal events. The differences were tested using the log-rank test. A two-tailed *P* value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, IL).

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Figure 1. Kaplan–Meier survival curves for (a) all fatal events and (b) cardiovascular deaths. DPZ, donepezil.

Table 1

Characteristics of the patient population studied

Characteristic	DPZ ⁺ (%) <i>n</i> = 76	DPZ ⁻ (%) <i>n</i> = 80
Follow-up time (months) ^a	29 ± 17	28 ± 25
Age ^a	80 ± 8	81 ± 8
<i>Sex</i>		
Female	51 (67.1)	54 (67.5)
Male	29 (38.2)	26 (32.5)
<i>Race</i>		
White	63 (82.9)	56 (70)
Nonwhite	17 (22.4)	24 (30)
<i>Diagnosis</i>		
Alzheimer's disease	67 (88.2)	64 (80)
Vascular dementia	9 (11.8)	16 (20)
<i>Chief complaint at time of admission</i>		
Orthopedic	13 (17.1)	12 (15)
Metabolic or nutritional	7 (9.2)	8 (10)
Cerebrovascular event	2 (2.6)	5 (6.3)
Other central nervous system disease	5 (6.6)	5 (6.3)
Cardiac event	14 (18.4)	12 (15)
Respiratory	21 (27.6)	10 (12.5)
GI tract	5 (6.6)	8 (10)

DPZ, donepezil; DPZ⁺, those who received donepezil medication; DPZ⁻, those who did not receive donepezil medication; GI, gastrointestinal.

^aValues are expressed as means ± SDs.

Table 2

Multivariate analysis of hazard ratios for fatal cardiovascular events and all fatal events

	Fatal CV events		All fatal events	
	Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
Donepezil medication	0.54 (0.30–0.98)	0.042	0.68 (0.46–0.99)	0.045
Vascular dementia	1.43 (0.69–2.99)	0.338	1.35 (0.82–2.21)	0.234
Age	1.03 (0.99–1.07)	0.095	1.02 (0.99–1.04)	0.151
Male	1.83 (1.03–3.23)	0.038	1.43 (0.97–2.12)	0.071
Nonwhite	1.40 (0.78–2.53)	0.261	1.30 (0.86–1.97)	0.212

CI, confidence interval; CV, cardiovascular.

Table 3

Outcomes in patients who received donepezil treatment and in those who did not

	DPZ ⁺ (%)	DPZ ⁻ (%)
Survivors	31 (40.8)*	10 (12.5)
Hospital admissions for cardiac events	10 (13.2)	17 (21.3)
<i>Fatal CV events</i>	18 (23.7)*	36 (45.0)
Ischemic heart disease	9 (11.8)	16 (20)
Other heart disease	5 (6.6)	12 (15)
Cerebrovascular diseases	8 (10.5)	4 (5)
<i>Fatal non-CV events</i>	27 (35.5)	34 (43.0)
Neoplasm	2 (2.6)*	14 (17.5)
Malignant solid neoplasm	2 (2.6)	5 (6.3)
Malignant, hematology, and lymph system	0 (0)	3 (3.8)
Malignant unknown neoplasm	0 (0)	6 (7.5)
Metabolic or nutrition	1 (1.3)	4 (5)
Diabetes mellitus	1 (1.3)	1 (1.3)
Lipid disorder	0 (0)	1 (1.3)
Volume depletion	0 (0)	2 (2.5)
Central nervous system	19 (25)*	7 (8.8)
Parkinson's disease	1 (1.3)	0 (0)
Alzheimer's disease	13 (17.1)	5 (6.3)
Unspecified dementia	4 (5.3)	2 (2.5)
Encephalopathy	1 (1.3)	0 (0)
Respiratory system	4 (5.3)	4 (5.0)
Pneumonia	2 (2.6)	3 (3.8)
Other chronic lower respiratory disease	2 (2.6)	0 (0)
Chronic obstructive pulmonary disease	0 (0)	1 (1.3)
Digestive system	0 (0)	4 (5)
Liver disease	0 (0)	2 (2.5)
GI bleeding	0 (0)	1 (1.3)
Cardiac disease	0 (0)	1 (1.3)
Renal system	1 (1.3)	0 (0)
Urinary tract infection	1 (1.3)	0 (0)
Other	0 (0)	1 (1.3)
Complications of medical and surgical care	0 (0)	1 (1.3)

CV, cardiovascular; DPZ, donepezil; DPZ⁺, those who received donepezil medication; DPZ⁻, those who did not receive donepezil medication; GI, gastrointestinal.

* $P < 0.01$ for comparisons between the DPZ⁺ and DPZ⁻ groups.