Acetylcholinesterase Inhibitor (Donepezil Hydrochloride) Reduces Heart Rate Variability

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Summary: An acetylcholinesterase inhibitor (donepezil hydrochloride) has recently been used for the treatment of senile dementia of Alzheimer type. The effect of this acetylcholinesterase inhibitor on the autonomic nervous control of the heart was investigated in 17 patients with senile dementia of Alzheimer type. Donepezil administration did not change the plasma concentration of norepinephrine or epinephrine. Twenty-four hour electrocardiogram monitoring was performed, and heart rate variability before and 6 weeks after treatment with donepezil (5 mg per orally) was determined. The heart rate averaged over 24 h was reduced slightly from 74.1 ± 2.7 beats/min before treatment to 71.1 ± 2.3 beats/min after treatment. Low (0.04–0.15 Hz) and high (0.15–0.40 Hz) frequency components were reduced significantly with treatment. Ultrasound (0.0001–0.003 Hz) and very low (0.003–0.04 Hz) frequency components were not affected. The reduction in the high frequency (41.9 ± 7.4%) component was greater (p < 0.03) than the reduction in the low frequency (18.6 ± 10.7%) component. It therefore appears that acetylcholinesterase inhibitor reduces the 1–30 s modulation of heart rate variability but that it has no influence on the much longer 1 min–1 h fluctuation. Key Words: Acetylcholine—Cardiac parasympathetic nerve—Catecholamine—Fractal characteristics—Phase-dependent effect.

The cardiac parasympathetic nerve controls the heart rate in various ways. It decreases the overall heart rate during tonic or tonic stimulation (cardio-inhibitory effect). It controls the heart rate precisely by periodic or phasic stimulation (phase-dependent effect) (1). A cardioinhibitory effect manifests in some conditions (2). The cardiac parasympathetic nerve also interacts with the sympathetic nervous system. A greater reduction in heart rate is produced with concurrent sympathetic stimulation than with parasympathetic stimulation alone (3,4). Onset and termination of the cardio-inhibitory effect are brief because the liberated acetylcholine in the synaptic cleft is hydrolyzed quickly by the abundant acetylcholinesterase in that space. When the cardiac parasympathetic nerve is stimulated in the tonic mode, the heart rate decreases with increases in the stimulation frequency. The number of impulses per unit of time defines the magnitude of the inhibitory effect. When the parasympathetic nerve is stimulated in the phasic mode, however, the effect is dependent on the time point at which the stimulus falls within the cardiac cycle. Acetylcholine released from the parasympathetic nerve ending hyperpolarizes the membrane of the sino-atrial (SA) node within the immediate cardiac cycle, and thus the next firing of the SA nodal cell is delayed (5). Beat-by-beat control of the heart rate is achieved by the phase-dependent mode of stimulation.

Donepezil hydrochloride, a potent acetylcholinesterase inhibitor, has been used for the treatment of senile dementia of the Alzheimer type (AD) (6). Orally administered donepezil might have an effect on other organs as well as the brain. It might also potentiate the cardiac effect of the parasympathetic nerve. We thus investigated the effect of donepezil on the cardiac parasympathetic control of the heart rate. The cardio-inhibitory and the phase-dependent effects, in particular, were investigated.

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METHODS

Subjects and study protocol

Patients with AD were recruited for the present study among in-patients treated at Tashirohigakai Hospital between 2000 and 2001. The AD was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (7) and the National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association for probable Alzheimer disease (8). Seventeen patients (six men, 11 women) participated. The mean age was 79.3 ± 2.7 years, and the mean body weight and height were 43.0 ± 1.8 kg and 1.48 ± 0.02 m, respectively. Essential hypertension was observed in five out of 17 patients. A calcium antagonist was administered for four patients, and an angiotensin-converting enzyme inhibitor for one patient. The calcium antagonist was also administered for a variant form of angina (one patient). All medications were kept constant during the study period. The ethics committee of Tashirohigakai Hospital approved the study protocol. Informed consent was obtained from the patient or a proxy in authority before participation in the study.

Before the administration of donepezil, the severity of dementia was quantified according to the Hasegawa Dementia Scale-Revised (HDSR) (9). Plasma concentrations of norepinephrine (NE), epinephrine (EPI), and dopamine were determined by high-performance liquid chromatography. Plasma renin activity and aldosterone and human atrial natriuretic hormone concentrations were determined by radioimmunoassay. Donepezil was administered at 3 mg/day in the morning for 2 weeks as a running-in period. After these 2 weeks, the dosage was increased to 5 mg/day, where it remained. One male patient was dropped from the study because of intolerance to the drug. Six weeks after the start of donepezil administration, the HDSR was applied again. Plasma concentrations of the various hormones were measured.

Twenty-four hour Holter electrocardiogram monitoring

Two-channel 24-h electrocardiogram (ECG) monitoring (Nihon Koden, Tokyo, Japan) was performed before and 6 weeks after the start of donepezil administration. The 24-h ECG signals were stored on a personal computer. Beat-by-beat cardiac cycle data were obtained by off-line computer analysis. The maximum entropy spectral analysis method (MemCalc; Suwa Trust, Tokyo, Japan) was used to calculate heart rate variability (HRV) (10). MemCalc possesses the superior reproducibility of the original time series over the fast Fourier transform and autoregressive methods. The total frequency (TF) considered was the 0.0001–0.5 Hz range. Four frequency bands of interest were considered: ultralow frequency (ULF), 0.0001–0.003 Hz; very low frequency (VLF), 0.003–0.04 Hz; low frequency (LF), 0.04–0.15 Hz; and high frequency (HF), 0.15–0.40 Hz. The complexity of HRV over minutes to hours was examined by plotting the log-transformed spectral amplitude against the log-transformed frequency between 0.0001 and 0.01 Hz. The slope of this line was taken as an index of the fractal component of HRV.

Statistical analysis

Values are presented as the mean ± SE. Differences in the mean responses before and after the administration of donepezil were examined by paired, two-tailed Student’s t test. A value of p < 0.05 was considered statistically significant.

RESULTS

HDSR scores improved slightly (from 9.1 ± 1.7 to 10.6 ± 2.1) with donepezil treatment, but the change was not statistically significant. Systolic blood pressure did not change significantly (from 125.0 ± 2.6 to 126.2 ± 3.6 mmHg), but diastolic blood pressure increased significantly from 69.4 ± 2.7 to 75.1 ± 2.3 mmHg (p < 0.02). Plasma concentrations of NE and EPI did not change significantly with treatment (Table 1). Neither was there a change in dopamine, plasma renin activity and aldosterone, or human atrial natriuretic hormone.

Twenty-four hour Holter ECG monitoring was completed successfully in 10 of the 16 patients; the mean monitoring time was 23 ± 0.5 h. The heart rate averaged over the 24-h period decreased slightly, but not significantly, from 74.1 ± 2.7 to 71.1 ± 2.3 beats/min. The TF power was 564.8 ± 1126.8 ms² before treatment and 686.3 ± 1368.9 ms² after treatment; the change was not significant. The ULF, VLF, LF, and HF components were expressed as percentages of the TF power. Both ULF and VLF did not change with treatment (Fig. 1A). The LF reduced significantly from 4.3 ± 1.1 to 3.4 ± 1.0% (p < 0.05) with treatment (Fig. 1B). The HF was also reduced significantly, from 3.5 ± 1.0 to 1.8 ± 0.5% (p < 0.03) with treatment. The LF/HF ratio increased significantly from 1.5 ± 0.2 to 2.0 ± 0.2 (p < 0.02; Fig. 2A). The changes between pre-treatment and post-treatment values were expressed as percentages, and were defined as reduction rates. The LF reduction rate was 18.6 ± 10.7%, and the HF reduction rate was 41.9 ± 7.4%

### Table 1. The effect of donepezil hydrochloride on various hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Before donepezil treatment</th>
<th>After donepezil treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (ng/ml)</td>
<td>0.42 ± 0.06</td>
<td>0.42 ± 0.09</td>
</tr>
<tr>
<td>Epinephrine (ng/ml)</td>
<td>0.04 ± 0.01</td>
<td>0.007 ± 0.004</td>
</tr>
<tr>
<td>Dopamine (ng/ml)</td>
<td>0.01 ± 0.005</td>
<td>0.008 ± 0.006</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml)</td>
<td>1.72 ± 0.75</td>
<td>1.23 ± 0.42</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>87.2 ± 12.4</td>
<td>87.4 ± 8.9</td>
</tr>
<tr>
<td>Human atrial natriuretic hormone (pg/ml)</td>
<td>85.6 ± 6.9</td>
<td>80.0 ± 6.0</td>
</tr>
</tbody>
</table>

Data presented as the mean ± SE for 16 patients.
FIG. 1. The effect of donepezil hydrochloride on heart rate variability. Four frequency bands of interest were examined before (open column) and after (filled column) treatment with donepezil: (A) ultralow frequency (ULF) and very low frequency (VLF) components; (B) low frequency (LF) and high frequency (HF) components. The bars at the tops of the columns represent one standard error of the mean.

FIG. 2. The effect of donepezil hydrochloride on (A) the low frequency/high frequency (LF/HF) ratio and (B) the reduction rate of LF and HF. The bars at the tops of the columns represent one standard error of the mean.

(Fig. 2B). The reduction in HF was significantly (p < 0.03) greater than the reduction in LF. The slope of the fractal component before treatment was -1.49 ± 0.09, and treatment did not change this significantly (-1.40 ± 0.07).

The reproducibility of HRV was tested in seven patients without Alzheimer's disease. The mean age at the first Holter ECG recording was 76.0 ± 1.8 years. The second recording was performed after 27.8 ± 12.8 weeks. The LF and HF components at the first recording were 3.54 ± 0.68 and 2.70 ± 0.73%, respectively; at the second recording, they were 3.09 ± 0.63 and 2.75 ± 0.72%, respectively. The values at the first recording did not statistically differ from those at the second recording. The ULF and VLF components also did not change with the passage of time.

DISCUSSION

Naturally occurring parasympathetic nerve impulses tend to cluster at a certain time point within the cardiac cycle (11,12). A single stimulus applied to the carotid sinus nerve leads to a discrete burst of activity in efferent parasympathetic fibers (13). Therefore, natural excitation of the cardiac parasympathetic nerve via sinoaortic baroreceptors might cause phase-dependent changes in the cardiac cycle length. Furthermore, the effect of the cardiac parasympathetic nerve is abrupt and it ends quickly. Thus, the parasympathetic nerve plays the major role in beat-by-beat variation. Both the ULF and VLF components represent the fluctuation between 2.8 h and 25 s, and LF represents that between 25 and 6.7 s. The HF band represents the fluctuation between 6.7 and 2.5 s.
Therefore, the HF component reflects beat-by-beat fluctuation of the heart rate to a greater degree than do the ULF and VLF components. The HF component reflects the variation more than even the LF component does. The HF component depends upon the phasic activity of the cardiac parasympathetic nerve and does not represent tonic activity of this nerve. In the present study, the acetylcholinesterase inhibitor reduced the HF component more than the LF component. The cardiac parasympathetic tone fluctuates beat-by-beat. The greater fluctuation in increased activity of the cardiac parasympathetic nerve would produce greater HF component power. As long as this relationship holds, the HF power is a good index of cardiac parasympathetic activity. The relationship may not hold, however, if the parasympathetic system is stimulated at a constant frequency (i.e., with no fluctuation) and if its effect is augmented at the SA node. Under these conditions, constant, successive prolongation of the cardiac cycle prevails. Simultaneously, beat-by-beat changes diminish. This means almost no deviation in the heart rate; HRV diminishes, as if parasympathetic nervous activity is absent. The decreased power of the HF component in the present study after administration of acetylcholinesterase inhibitor suggests that the phase-dependent effect is reduced.

The increased LF/HF ratio we observed after treatment with the acetylcholinesterase inhibitor probably reflects the greater reduction in the HF component over that in the LF component. It may not reflect the enhanced sympathetic nervous activity. This is supported by the fact that the plasma NE and EPI concentrations remained stable after administration of the acetylcholinesterase inhibitor. The acetylcholinesterase inhibitor does not affect long-term fluctuation (minutes to hours) of the heart rate, or even that over a longer period. A steep slope in the fractal component has been considered recently as a risk factor for death from cardiovascular causes (14,15). The acetylcholinesterase inhibitor also preserves the fractal nature of HRV. Aging reduces the LF and HF components linearly (16–19). Furthermore, the LF and HF components in AD are low in absolute value (20). The mean age was 79 years in the present study. Therefore, normalized LF and HF components might be low.

The acetylcholinesterase inhibitor slowed the overall heart rate slightly in the present study. Systemic injection of phystostigmine has been shown to decrease the heart rate in rats, as have other acetylcholinesterase inhibitors such as tacrine and rivastigmine (21,22). The bradycardic effect has been shown to be mediated by a peripheral muscarinic mechanism, since bradycardia is abolished by peripheral administration of methylatropine and atropine but is not influenced by centrally administered atropine. By slowing the degradation of acetylcholine in the synaptic cleft, acetylcholinesterase inhibitor potentiates the bradycardic response evoked by tonic activation of the cardiac parasympathetic nerve in dogs (23). The dosage regimen we followed in the present study might be low (5 mg, per orally) in comparison with that of our previous experiment (12.9 mg, intravenously, as a total dose adjusted to body weight of 43 kg) (23). In addition, the present patients were considered under physiological conditions rather than under the influence of experimentally augmented parasympathetic activity. Therefore, a slight decrease in the heart rate emerged in the present study.

In the present study, the diastolic blood pressure was significantly increased by 6 mmHg. Systemic injection of phystostigmine and tacrine increased the arterial blood pressure (21,22). Atropine abolished the tacrine pressor response but methylatropine did not. Therefore, the increase in diastolic blood pressure may be produced by the central action of donepezil. The small increase in arterial blood pressure may increase the parasympathetic nerve activity through baroreceptor activation and it may increase HRV a little. This effect was opposite of the donepezil effect observed in the present study. Clinically important implications can be obtained as a sequel to the increase of diastolic blood pressure. For AD with hypertension, the administration of donepezil might require caution. An approximately 6 mmHg rise in diastolic blood pressure should be borne in mind as these patients may need strict control of hypertension. The reduced HRV, especially the LF and HF components, after donepezil administration may suggest a more tightly controlled heart rate than before donepezil administration. The vaso-vagal reflex is the dangerous reflex, producing severe bradycardia and hypotension. A tightly controlled heart rate may prevent the occurrence of vaso-vagal reflex.

In conclusion, the acetylcholinesterase inhibitor has only a small effect on the overall heart rate. However, it has a significant effect on HRV, especially the HF component. The acetylcholinesterase inhibitor at clinical doses may reduce the beat-by-beat fluctuation evoked by cardiac parasympathetic nervous activity. It may be more powerful clinically in reducing the phase-dependent effect rather than in potentiating the tonic inhibitory effect.

REFERENCES


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