RAPID COMMUNICATION

IMPROVED AUTONOMIC NEUROCARDIAL BALANCE IN SHORT-TERM ABSTINENT ALCOHOLICS TREATED WITH ACAMPROSATE

M. W. AGELINK*, W. LEMMER, R. MALEŠA1, T. ZEIT, T. MAJEWSKI2 and E. KLIESER2

Departments of Psychiatry and 2Internal Medicine, Evangelical Hospital Gelsenkirchen, University of Bochum and 1Department of Neurology, University of Jena, Germany

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Abstract — Standardized investigations on resting heart rate variability (HRV) should provide more information on acamprosate's human pharmacodynamic properties because acamprosate interacts with several neurotransmitter systems which are also involved in maintaining autonomic neurocardiac balance. We performed HRV measurements prospectively in 69 healthy controls and 19 chronic alcoholics to prove the hypotheses that: (1) compared to healthy controls, chronic alcoholics show disturbances in neurocardiac vagal function; and (2) in alcoholics, acamprosate treatment (6-8 days) should further decrease parasympathetic activity if acamprosate interacts with central γ-aminobutyric acidA receptors in vivo. Cardiovagal dysfunction was initially present in 21% of the alcoholics. After treatment, however, their neurocardiac sympathetic–parasympathetic balance improved significantly.

INTRODUCTION

Acamprosate (calcium acetylhomotaurinate), a synthetic compound similar to γ-aminobutyric acid (GABA), reduces drinking relapse in detoxified alcoholics. However, its pharmacodynamic properties in man and the mechanisms underlying its action remain unclear (Littleton, 1995). Significant methodological problems in elucidating acamprosate's mechanisms of action in man exist as specific indicators for the various possible neurotransmitter actions involved are lacking. Standardized investigations on resting heart rate variability (HRV), including power spectral analysis, should provide more information on acamprosate's pharmacodynamic properties in man, because acamprosate may interact with several neurotransmitter systems which are also involved in maintaining autonomic neurocardiac balance. The integrity of autonomic neurocardial function is influenced by cholinergic, serotonergic, adrenergic, and GABAergic mechanisms. Acamprosate lacks cholinergic properties; however, stimulation of central serotonergic activity and antagonism of noradrenergic activity have been proposed (summary in Wilde and Wagstaff, 1997). The GABAergic effects of acamprosate have been shown in both animals (Boismare et al., 1984; Chabenat et al., 1988; Daoust et al., 1992) and man (Gerra et al., 1992). However, newer in vitro receptor binding studies on human embryonic kidney cells indicate that acamprosate does not bind to GABA_A receptors (Ziegglansberger et al., 1996). Stimulation of central GABA_A receptors can disturb the autonomic neurocardial balance significantly; due to their GABA-agonistic activity, benzodiazepines produce vagolytic effects in both animals and man by potentiating the tonic inhibition of cardiac vagal input (DiMicco, 1987; Vogel et al., 1996). Thus, if acamprosate stimulates GABA_A receptors in the central nervous system, disturbances in cardiovagal function would follow.

Standardized measurements of the resting heart rate variability (HRV) using spectral analysis allow a quantitative assessment of the sympathetic–parasympathetic balance of neurocardial
regulation under steady-state conditions without requiring active patient co-operation. In the present study, the HRV was compared: (1) between healthy individuals and alcohol-dependent patients; and (2) among alcoholics before and after 6.8 days (on average) of treatment with acamprosate. We hypothesize that (1) compared to healthy controls, chronic alcoholics should show disturbances in cardiovagal function associated with decreases in parasympathetic activity (Villalta et al., 1989; Rechlin et al., 1996) and (2) acamprosate should further decrease parasympathetic activity if it interacts with central GABA_A receptors in vivo.

METHODS

Alcoholics with secondary somatic and mental diseases known to affect HRV measurements were excluded from the study; these included heart or lung disease, liver cirrhosis, hepatitis, pancreatitis, thyroid gland dysfunction, diabetes mellitus, malnutrition, multiple drug dependence (including chloromethiazole abuse), depression, anxiety disorders, and schizophrenia. Data from 19 alcoholics diagnosed according to DSM-III-R criteria (American Psychiatric Association, 1987) (11 men, 8 women; mean age ± SD 42.4 ± 8.1 years; range 28–63 years), who passed the strict selection criteria and gave informed consent to undergo repeated HRV measurement, were available for analysis. Detailed neurological examination revealed signs of peripheral neuropathy in 13 alcoholics, whereas none had other alcohol-related neuropathologies (e.g. Korsakoff’s psychosis, Wernicke’s encephalopathy). Patients’ alcohol-related variables were as follows: Munich Alcoholism Test, total score 34.6 ± 8.4 (range 18–47); daily alcohol intake over 4 weeks before admission 287 ± 129 g/day (range 80–560 g/day); duration of alcohol dependency 12.7 ± 8.1 years; total life-time dose of alcohol 1444 ± 1191 kg. The extent of liver damage was shown by increased plasma levels of γ-glutamyltransferase 226.7 ± 227.1 U/l (pathological in 13 of 19 cases).

The control group consisted of 69 healthy volunteers. Controls did not drink regularly; their average alcohol intake was less than 20 g/day. There were no statistically significant differences in demographic variables between patients and controls.

In alcoholics, baseline HRV measurements were made 8 days after they had finished an alcohol detoxification programme in isolation. At the time of investigation, all were medication-free, cardiopulmonarily stable, and showed no withdrawal symptoms. Since steady-state levels of acetylhomotaurinate were achieved by the seventh day of dosing (Durbin et al., 1996), repeated examinations were performed after 6–8 days of acamprosate treatment (average 6.8 days, daily oral doses of 3 × 666 mg).

To avoid circadian variation effects, subject measurements were always performed between 09:00 and 11:00 a.m. The measurement and evaluation of HRV were performed as described elsewhere (Ziegler et al., 1992; Rechlin et al., 1996). The artefact-free digitalized electrocardiogram recordings were stored for later analysis using the software package Neurodiag (ProSciCare update developed by H. Lambeck, Munich, Germany). The resting heart rate (HRr) was the average rate measured during the 5-min HRV analysis. The coefficient of variation (CV) was the standard deviation of the R-R intervals divided by their average duration; this parameter described parasympathetic activity (the root mean square of successive differences, RMSSD). Also served this purpose). A 5-min period of artefact-free R-R intervals recorded at 1 ms resolution was converted by a mathematical algorithm (Berger et al., 1986) to a discrete signal of 1024 possible levels (samples at 290-ms intervals) for spectral analysis. The resulting power spectrum was processed by a Fast-Fourier transformation, whereby the frequency bands were automatically separated: low-frequency-band (LF; 0.01–0.05 Hz); mid-frequency-band (MF; 0.05–0.15 Hz); high-frequency-band (HF; 0.15–0.50 Hz). The HF band correlates closely with parasympathetic activity, whereas the LF bands are affected primarily by vasomotor influences, sympathetic influences, and baroreceptor activity.

Statistics

Multivariate analysis (MANCOVA) was performed with group (alcoholics vs controls) as an independent factor, the HRV parameters (at baseline) as dependent variables, and age as the covariate. HRV parameters at two measurement time points were compared using the Wilcoxon test. Normal values for HRV were provided by the
Table 1. Heart rate variability in healthy controls and alcoholics under baseline conditions and after treatment with acamprosate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 69)</th>
<th>Total group</th>
<th>Alcoholics (n = 19)</th>
<th>After acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRr (beats/min)</td>
<td>72.4 ± 11.8; 72.8</td>
<td></td>
<td>77.1 ± 13.6; 79.6</td>
<td>76.4 ± 11.4; 75.1</td>
</tr>
<tr>
<td>CV (%)</td>
<td>(49.0–99.5)</td>
<td>(58.5–95.8)</td>
<td>(3.9 ± 1.7; 3.5</td>
<td>(55.7–97.3)</td>
</tr>
<tr>
<td>RMSSDr (ms)</td>
<td>4.8 ± 1.9; 4.7</td>
<td>(1.9–10.8)</td>
<td>(1.4–8.4)</td>
<td>(1.8–7.7)</td>
</tr>
<tr>
<td>Spectral analysis (Hz²)</td>
<td>31.9 ± 20.8; 24.4</td>
<td>(6.9–99.4)</td>
<td>26.8 ± 21.4; 15.4</td>
<td>26.9 ± 18.9; 21.0</td>
</tr>
<tr>
<td>LF power</td>
<td>3.24 ± 2.85; 2.21</td>
<td></td>
<td>2.25 ± 1.67; 1.57</td>
<td>2.94 ± 2.90; 1.67</td>
</tr>
<tr>
<td>MF power</td>
<td>(0.44–14.17)</td>
<td>(0.81–6.12)</td>
<td>(0.33–8.88)</td>
<td>(0.35–10.29)</td>
</tr>
<tr>
<td>HF power</td>
<td>3.90 ± 4.60; 2.02</td>
<td></td>
<td>2.35 ± 2.11; 2.20</td>
<td>3.17 ± 3.07; 1.98</td>
</tr>
<tr>
<td>(LF/HF) ratio*</td>
<td>(0.43–24.05)</td>
<td>(0.33–8.88)</td>
<td>(0.23–10.60)</td>
<td>(0.19–15.43)</td>
</tr>
<tr>
<td></td>
<td>3.76 ± 6.69; 1.42</td>
<td></td>
<td>2.20 ± 2.74; 0.69</td>
<td>2.98 ± 3.63; 1.68</td>
</tr>
<tr>
<td></td>
<td>(0.39–27.32)</td>
<td>(0.23–7.59)</td>
<td>(0.19–15.43)</td>
<td>(0.19–15.43)</td>
</tr>
<tr>
<td></td>
<td>1.95 ± 1.92; 1.64</td>
<td></td>
<td>2.71 ± 2.85; 1.74</td>
<td>1.92 ± 2.18; 1.47</td>
</tr>
<tr>
<td></td>
<td>(0.29–11.00)</td>
<td>(0.12–10.10)</td>
<td>(0.18–9.02)</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as mean ± SD; median (range). LF, low frequency; MF, mid frequency; HF, high frequency. *Mean of the individual LF/HF ratios from each patient.

69 healthy controls; values lower than the 2.3 percentile points of the controls were considered as pathological (Ziegler et al., 1992).

RESULTS

Table 1 summarizes the mean HRV values. Compared to healthy controls, alcoholics showed a trend towards a reduced CV (MANCOVA; 1,85 df; \( F = 3.08; \ P = 0.083 \)). Pathologically reduced baseline HRV parameters were shown by four of 19 alcoholics (1 × CV, 1 × RMSSDr, 2 × MF power and 3 × HF power). The mean systolic and diastolic blood pressure did not differ between patients and controls. Treatment with acamprosate normalized the initially raised (in comparison to normals) LF/HF ratio (\( P < 0.05 \)). At the second measurement point, pathological HRV parameters were observed in two of the 19 alcoholics (2 × MF and 1 × HF power). Blood pressure did not change significantly.

DISCUSSION

Of the alcoholics investigated, 21% showed pathological parasympathetic HRV parameters (CV, RMSSDr, HF power) indicating cardiovagal dysfunction (CVD), a figure agreeing with CVD frequencies of 20–28% reported elsewhere (Johnson and Robinson, 1988; Villalta et al., 1989; Rechlin et al., 1996).

Contrary to our original hypothesis, no further deterioration in the sympathetic–parasympathetic balance was found after the (on average) 6.8 days of treatment, but rather an improvement (normalization of the initially raised LF/HF ratio; lowered frequency of pathological measurements). This suggests that acamprosate does not interact significantly with GABA\(_A\) receptors in man, and agrees with clinical experience where no psycho-tropic adverse reactions during or withdrawal symptoms after acamprosate therapy were observed (Paille et al., 1995; Sass et al., 1996).

A non-placebo controlled, non-randomized study is limited and as such the possibility that the HRV improvement was spontaneous cannot be ruled out: significant improvements in HRV after alcohol abstinence for about 1 year (Villalta et al., 1989), 6 months (Weise et al., 1986) or 12 weeks (Hirsch et al., 1993) have been shown using a variety of autonomic tests. In our study, a normalization of an initially existing neurocardiac imbalance could already be shown after 6.8 days (on average) of treatment with acamprosate: hence we suspect that the effect was not exclusively due to spontaneous changes in neurocardiac regulation. As such, it can be speculated that acamprosate directly influences the central cardiovascular...
regulation centres, or that other mechanisms of the drug’s action are brought into play which indirectly normalize an initially existing sympathetic–parasympathetic imbalance.

Ben-David and Zipes (1988) emphasized that the integrity of the cardiac autonomic nervous system is important in preventing, promoting or precipitating cardiac arrhythmias and sudden cardiac death. As in the case with diabetics, the presence of a CVD is associated with an increased cardiovascular mortality rate among alcoholics (Johnson and Robinson, 1988). Hence acamprosate may contribute to reducing cardiovascular mortality risk through its effects on neurocardial regulation; this represents an interesting point for future longitudinal studies which investigate the effects of acamprosate during alcohol withdrawal and rehabilitation.

REFERENCES


