ALCOHOL CONSUMPTION, %CDT, GGT AND BLOOD PRESSURE CHANGE DURING ALCOHOL TREATMENT

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Abstract — Aims: Blood pressure (BP) changes in alcohol-dependent individuals during a 12-week alcohol relapse prevention study were examined in light of drinking status and biomarkers of alcohol consumption [carbohydrate-deficient transferrin (%CDT) and gamma-glutamyl transpeptidase (GGT)]. Methods: Of 160 randomized alcoholic individuals, 120 who had hypertension and in whom daily drinking data was available, at 6 and 12 weeks of treatment were included. The impact of alcohol consumption on change in systolic BP (SBP) and diastolic BP (DBP) was examined. Further analysis determined the relationship between BP and alcohol-use biomarkers. Results: A significant effect of complete abstinence on both SBP (−10 mmHg; \textit{P} < 0.003) and DBP (−7 mmHg; \textit{P} = 0.001) when compared to any drinking (SBP and DBP \textit{P} = 0.01) was observed. At week 12, participants with a positive %CDT (≥ 2.6) had 7 mmHg greater SBP (\textit{P} = 0.01) and DBP (\textit{P} < 0.001) than those with negative %CDT. Participants with positive GGT (≥ 50 IU) had 10 mmHg greater SBP (\textit{P} = 0.12) and 9 mmHg greater DBP (\textit{P} = 0.03) than those with negative GGT. The percent change in SBP was correlated with percent change in %CDT (\textit{P} = 0.003) but not GGT (\textit{P} = ns). The percent change in DBP was correlated with both percent change in %CDT (\textit{P} < 0.0001) and GGT (\textit{P} = 0.03). Conclusions: Abstinence from alcohol significantly decreased the BP and a positive relationship between BP and both alcohol-use biomarkers was illustrated. Since %CDT is more specific than GGT for heavy alcohol consumption, clinicians may monitor the role of alcohol in hypertension using %CDT as a supplemental aid, providing an objective assessment of drinking to influence BP treatment decisions.

INTRODUCTION

High blood pressure (BP) is an important cause of morbidity and mortality. It is the leading cause of stroke and heart failure, as well as the second most common precursor to end-stage renal disease (US Department of Health and Human Services, 2003). Identified risk factors for high BP include advanced age, obesity, excess sodium intake, physical inactivity and, important to this article, excessive alcohol consumption (Whelton \textit{et al}., 2002).

The relationship between BP and alcohol consumption is somewhat complex. Light to moderate alcohol consumption has been associated with reduced risk for coronary heart disease (CHD) and subsequent reduction in total mortality (Shaper \textit{et al}., 1994; Di Castelnuovo \textit{et al}., 2002; Mukamal \textit{et al}., 2003). However, heavy alcohol consumption (≥ four standard drinks/day for females and ≥ five standard drinks/day for males) is clearly associated with increased BP. The association between ‘heavy’ alcohol intake and increased BP in males and females appears to be independent of other factors, including obesity and smoking (Campbell \textit{et al}., 1999). Recommendations for the treatment of high BP include decreased alcohol consumption, if not complete cessation. It is advised that hypertensive individuals limit their alcohol intake to no more than two-drinks a day for men and one-drink a day for women (US Department of Health and Human Services, 2003).

Frequently, clinicians do not identify alcohol as being etiologic in high BP, leading to the prescription of anti-hypertensive medications without addressing alcohol consumption. Possible explanations include clinician’s concern about offending patients by asking about alcohol consumption (Kaariainen \textit{et al}., 2001), practitioner time constraints, and patients’ hesitancy to provide accurate drinking information. Nevertheless, alcohol consumption assessment can be crucial for successful treatment.

Even with pharmacological treatment, only 50% of hypertensive patients are able to achieve and maintain their BP at or below health-targeted limits (Hajjar and Kotchen, 2003). Heavy alcohol consumption may be an important cause of treatment-resistant hypertension, potentially by interfering with the pharmacological action of anti-hypertensive medications and with adherence to physician recommendations designed to treat high BP (Miller \textit{et al}., 2005).

A common concern in clinical practice is the inconsistency between a patient’s self-reported alcohol consumption and actual alcohol consumption. Under these conditions, laboratory markers of alcohol consumption can play an important role in identifying alcohol-induced clinical conditions including hypertension. Gamma-glutamyl transpeptidase (GGT), %carbohydrate-deficient transferrin (%CDT), and their combination are increasingly being used to detect heavy drinking and provide objective markers of risk for alcohol-related diseases (Fleming and Mundt, 2004; Miller, 2004; Miller \textit{et al}., 2006). Serum GGT levels of ≥ 50 IU are associated with significantly higher BP as well as with a diagnosis of hypertension (Sillanaukee \textit{et al}., 1998). Sillanaukee and colleagues have demonstrated a significant association between BP and a mathematical combination of GGT and %CDT (Sillanaukee \textit{et al}., 2001). The relationship between %CDT and BP requires further clarification, as other authors have reported a positive relationship between elevated GGT level and CHD, but an inverse relationship between elevated CDT level and CHD (Jousilahti \textit{et al}., 2002). As %CDT is a specific marker of heavy alcohol consumption, higher %CDT values alone may also be associated with higher BP and a reduction of %CDT during attempts at alcohol reduction might predict lower BP. Many individuals entering alcohol treatment...
centers have elevated BP and it is unclear if this increase in BP is reflective of acute alcohol withdrawal or chronic high alcohol use. Therefore, evaluating BP in newly abstinent alcoholics over time using state-of-the-art drinking assessment could address this issue as well.

This report evaluates individuals participating in a clinical alcohol relapse prevention trial independent of their BP. The aims of the study were to (i) evaluate changes in BP over time in relation to changes in drinking status and (ii) examine the relationship between biological markers of alcohol consumption and BP changes over time.

MATERIALS AND METHODS

Recruitment and baseline assessment
Subjects included alcohol-dependent participants in a randomized clinical trial that investigated naltrexone combined with either cognitive behavioural or motivational enhancement therapy for alcohol dependence (Anton et al., 2005). Participants were seeking outpatient treatment for alcoholism. The participant recruitment, inclusion/exclusion criteria, and baseline assessments are described in detail elsewhere (Anton et al., 2005). Briefly, all subjects were dependent on alcohol but not on other substances (except nicotine), did not have other major psychiatric diagnoses, and were medically stable. Liver enzymes (ALT, AST) of all participants had to be less than 2.5 times the upper limit of normal at the time of randomization.

Study procedures
Randomized subjects (N = 160) were evaluated for alcohol and substance abuse by a technician at baseline and at the end of weeks 2, 6, and 12. BP (while seated), blood for liver function tests (ALT and AST) and biomarkers of alcohol consumption (%CDT and GGT), and measurements of alcohol consumption (see below) were obtained at each of these visits. BP was taken via the same electronic BP monitoring device (DINAMAP ProCare 120) that was calibrated every 6 months for accuracy.

Measurement of alcohol consumption
Daily alcohol consumption was measured by a calendar-based self-report procedure, the time line follow-back method, reported to be accurate over a number of months retrospectively (Sobell et al., 1988; Sobell and Sobell, 2000). In this method, each individual indicated how much he/she drank on each day during a specified period of time (7–90 days) on a calendar uniquely structured for that study visit. Mnemonics such as special dates and events are put on the calendar to assist in this process. Also, in our hands, a set of standard-sized glasses are provided into which the subject pours water from a picture to indicate their usual drink size. The volume is subsequently measured and converted into standard drinks (12 oz beer (4–5% alcohol), 5-oz wine, or 1.5-oz spirits (40% alcohol). This method was used to quantify daily alcohol consumption for the 30 days prior to study participation and during the study as indicated above. This method has been utilized in the most advanced treatment trials e.g. the COMBINE Study (Anton et al., 2006).

Biological assays
%CDT was measured via micro-column separation and Elisa assay method (Anton et al., 2001) using test kits purchased from Biorad Inc. (Hercules, CA) at the Clinical Neurobiology Labs at the Medical University of South Carolina (Raymond F. Anton, M.D., Director). Inter- and intra-assay coefficients of variation are below 10%. GGT was measured via Abbott (Santa Clara, CA) Aeroset auto-analyser using standard reagents and controls with inter- and intra-coefficient of variations below 5%.

Statistics
Data were derived from 120 of the 160 participants in the alcohol treatment clinical trial (Anton et al., 2005), irrespective of treatment group assignment, and for whom a BP reading at the 12-week research period was available. All analyses were conducted using the Statistical Package for Social Sciences (SPSS 11.5 analytic package). Baseline variables (age, gender, ethnicity, marital status, alcohol dependence scale score, drinks per drinking day past 90-days, %days of heavy drinking past 90-days, standard drink units past 90-days, BMI, and nicotine use) were examined for predictive validity of pre-study SBP and DBP by linear regression analysis. During the trial the impact of drinking status on BP at week 12 and the relationship of biomarkers (%CDT and GGT) to BP were analysed by ANCOVA (using study entry BP as a covariate). Non-parametric analysis (Spearman’s Rho) was used to determine the relationship between percent (week 12 baseline x100%) change in BP, GGT, and %CDT over the course of 12 weeks.

RESULTS

Demographic and baseline characteristics of the 120 participants providing data on BPs at week 12 were similar to those of the intent to treat analysis participants (N = 160) (Anton et al., 2005) (Table 1). Subjects were mostly Caucasian, male,

<table>
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<tr>
<th>Table 1. Demographics of study sample (N = 120)</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Gender (% male)</td>
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<tr>
<td>Ethnicity (% Caucasian)</td>
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<tr>
<td>% Married</td>
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<tr>
<td>Alcohol dependence scale</td>
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<tr>
<td>Drinksa per drinking day past 90-days</td>
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<tr>
<td>% Days heavy drinkingb past 90-days</td>
</tr>
<tr>
<td>Standard drink units past 90-days</td>
</tr>
<tr>
<td>Body Mass Index</td>
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<tr>
<td>Nicotine use</td>
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a A drink is defined as 12 oz of beer, 1.5 oz of liquor or 5 oz of wine.

b A heavy drinking day is ≥five drinks for men or ≥four drinks for women.
and married, drinking 12 ± 6 drinks per drinking day over the 90-days prior to randomization with an average of 74% of those drinking days being heavy drinking days.

Linear regression analysis indicated that gender (P = 0.02) was a predictor of DBP at baseline while increasing age (P = 0.03) was associated with higher baseline SBP. BMI was significantly correlated with SBP (r = 0.28, P = 0.002) and DBP (r = 0.24, P = 0.009). Ethnicity, marital status, alcohol dependence scale score, drinks per drinking day past 90-days, %days heavy drinking past 90-days, standard drink units past 90-days, and nicotine use were not significantly related to BP.

The impact of total abstinence versus any drinking on BP during the 12 weeks of treatment is shown in Table 2. Total abstinence during the 12-week treatment period reduced SBP by 10 mmHg (P = 0.003) and DBP by 7 mmHg (P = 0.001). In comparison, those who reported any drinking had only a 1 mmHg reduction in SBP and DBP, respectively.

<table>
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<th>Table 2. Impact of drinking status on blood pressure during trial at week 12 (end of treatment)</th>
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<tr>
<td>Any drinking (N = 74)</td>
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<td></td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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</table>

* P = 0.003 compared to any drinking. ** P = 0.001 compared to any drinking.

The levels of both SBP and DBP, and those of biological markers (%CDT and GGT) at weeks 0, 6, and 12 are shown in Table 3. BP and both biological markers of alcohol consumption, demonstrated a significant reduction over time (P < 0.001). Reductions in %CDT and GGT were the most pronounced between week 0 and week 6 (P < 0.001), the period that saw the greatest reduction in both SBP and DBP. A significant overall increase in %CDT was observed between week 6 and week 12 (P < 0.001), which is consistent with previous data indicating the timeframe of increasing drinking for those who relapse (Anton et al., 1996; Myrick et al., 2001; Anton et al., 2002).

To address the issue of relapse, participants with normal or high biological variables at week 12 were examined separately. Table 4 shows the relationship of BP to %CDT and GGT status at week 12. Participants with negative (normal) %CDT (<2.6%) or negative (normal) GGT (<50 IU) had significantly lower BPs than those with positive (high) %CDT or positive (high) GGT. There was a significant difference between positive and negative %CDT (df1, F = 6.73, P = 0.01) on SBP. There was a significant difference between positive and negative %CDT (df1, F = 9.35, P = 0.03) and GGT (df1, F = 4.62, P = 0.03) on DBP. The highest BP (SBP = 142 ± 20; DBP = 88 ± 13) was observed in participants that had both positive %CDT and positive GGT (N = 18).

The relationship between change in SBP and DBP and change in %CDT and GGT between baseline and week 12 is illustrated in Fig. 1. There was a significant relationship between the magnitude of change of %CDT and magnitude in change of both SBP (P = 0.003, Rho = 0.28) and DBP (P < 0.0001, Rho = 0.34). Figure 1 panels A and B illustrate that those with a greater reduction in %CDT had a greater reduction in both SBP and DBP, while those with a greater elevation in %CDT had a corresponding greater increase in SBP and DBP. A significant association between the magnitude in GGT change and both SBP (P > 0.05, Rho = 0.09) and DBP (P = 0.03, Rho = 0.20) change was observed, but this was only significant for DBP. Figure 1 panels C and D show that those who had a greater reduction in GGT had a greater reduction in SBP and DBP, while those who had a greater increase in GGT had a greater elevation of SBP and DBP.

During the baseline assessments and at the end of study interview (week 12) 17 of the 120 participants reported being prescribed and ingesting medications used to treat hypertension (anti-hypertensives). The demographics of the 17 participants prescribed and ingesting antihypertensive medications during the trial were not different than that of the other 103 participants. Of the 17 participants who had prescribed BP medication, 7 reported total abstinence and 10 reported drinking during the 12-week treatment period. The general direction of a reduction in both SBP (−9 mmHg in those who were abstenent and −4 mmHg in those who were drinking) and DBP (−4 mmHg in those who were abstenent and −1 mmHg in those who were drinking) was seen. However, this reduction from baseline was not significant, secondary to the small sample size. Although the 17 participants taking prescribed BP medications had higher, but not significantly higher, SBP and DBP throughout the trial, the relationship between BP and biomarkers was the same as the rest of the participants.
Table 4. Blood pressure in relation to positive or negative % carbohydrate-deficient transferrin (%CDT) and gamma-glutamyl transpeptidase (GGT) at week 12 (end of treatment)

<table>
<thead>
<tr>
<th></th>
<th>Positive %CDT</th>
<th>Negative %CDT</th>
<th>Positive GGT</th>
<th>Negative GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>66</td>
<td>30</td>
<td>87</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137 ± 18(^b)</td>
<td>130 ± 15(^c)</td>
<td>140 ± 18</td>
<td>130 ± 16</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83 ± 12(^c)</td>
<td>76 ± 11(^c)</td>
<td>85 ± 12(^d)</td>
<td>76 ± 11(^d)</td>
</tr>
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\(^a\) Positive CDT = (≥ 2.6%), positive GGT (≥ 50 IU). Negative refers to values within the non-drinking range of normal. \(^b\) \(P = 0.01\). \(^c\) \(P < 0.001\). \(^d\) \(P = 0.03\).

Fig. 1. Percent change in systolic and diastolic blood pressures in relation to percent change in % carbohydrate-deficient transferrin (%CDT) (panels A and B) and gamma-glutamyl transpeptidase (GGT) (panels C and D) between weeks 0 and 12.

DISCUSSION

This study used state-of-the-art methods (both verbal reporting and biological) to assess drinking over time in recently abstinent alcoholics. While this should lend credence to the findings reported, it is possible that alcohol consumption might have not been completely reported or recorded. The goal of this study was not to monitor BP. It was a naturalistic representation of what would occur when heavy drinking/alcohol-dependent individuals attempt to abstain from alcohol, and during relapse drinking. As such, it provided an opportunity to access how BP changed free of medical treatment bias.

This study shows that reduction in alcohol consumption in heavy drinkers was associated with reductions in both BP and biological markers of alcohol consumption over the course of the trial. This supports previous work demonstrating that reductions in alcohol consumption result in reductions in BP (Marmot et al., 1994; Xin et al., 2001). When drinking status was taken into account, those participants who maintained total abstinence for the duration of the 12-week clinical trial had a 10 mmHg reduction in SBP and a 7 mmHg reduction in DBP when compared to those with any drinking. The direction and magnitude of the BP changes was similar in those who were and were not currently prescribed antihypertensive medications. These results support recommendations for abstinence as a means to reduce BP in alcohol-dependent individuals. While state-of-the-art measures were utilized to assess drinking, it is still possible that participants who reported only minor drinking during the study had much more consumption than actually reported, leading to more elevation of BP than would be expected from only minor breaches of abstinence.

As there are frequent inconsistencies between self-reported and actual alcohol consumption (Simpura, 1987), biological indicators of heavy alcohol consumption can play a critical role in identifying heavy alcohol consumption as a contributing factor to high BP, more so in primary care clinics. Consistent with previous findings, this study illustrates a positive correlation between BP and GGT (Saunders et al., 1981; Lee et al., 2002; Stranges et al., 2005). Others have suggested that elevated GGT may be a predictor for hypertension in...
drinking as it may reflect individual susceptibility to the BP-raising effect of alcohol (Lee et al., 2002). Serum GGT has been hypothesized to be not only an indicator of heavy alcohol consumption but also a marker of cardiovascular risk (along with total cholesterol, triglyceride, fasting plasma glucose, total homocysteine, and SBP) or oxidative stress (Sakuta et al., 2005). In fact, heavy alcohol consumption might play an intermediary role in a number of these risk factors through hepatic pathology that might be reflected in elevated GGT release and blood levels.

An advantage of %CDT is its superior specificity in detecting heavy alcohol consumption (over 90%) (Miller et al., 2004). We found that increased %CDT levels were associated with increases in both SBP and DBP, whereas increased GGT levels were associated with only an increase in DBP. This is of utmost importance since the specificity of %CDT could provide a clinician much more confidence in identifying recent heavy alcohol as a contributing cause of high BP when used either alone or possibly in conjunction with GGT.

Further investigation into the relationship between BP and biomarkers led to the finding of a significant association between percent change in %CDT and BP as well as percent change in GGT and BP (Fig. 1). The majority of participants had BP and biomarker readings that placed them in the lower left quadrant of each figure, indicating that as the value of the biomarker decreased so did BP, consistent with the drinking data. A disconnect between the biomarkers and BP is present in the upper left quadrant of each figure (as the value of the biomarker increased, the BP dropped). A possible explanation for this could be that these participants began, or resumed taking a BP medication, resulting in a reduction in BP even though they continued to drink heavily. An alternative explanation would be that the biomarkers were responding to a level of drinking that did not cause BP elevation. Those in the lower right quadrant of each figure, where BP increased as the biomarker decreased, either had high BP unrelated to alcohol consumption or had unresponsive alcohol consumption biomarkers (which might occur in 30–40% of participants—particularly at lower levels of drinking). Finally, those in the upper right quadrant of each figure, where BP increased as biomarker increased, continued to consume alcohol in moderate to heavy levels throughout the duration of the trial (irrespective of verbal reports).

The strength of this study was the rigour with which the drinking data were obtained. A limitation of the study is that only three BP readings (at baseline, week 6, and week 12) were included. This prevents investigating a more detailed relationship between drinking status and acute changes in BP. We must acknowledge that BPs were obtained from an automatic BP machine, however the machine was calibrated and routinely checked and maintained. An important future direction will be a more detailed investigation of BP reduction in light of reduction in alcohol consumption. The detailed drinking information that was collected in the alcohol treatment trial allows a unique opportunity to explore this relationship in even greater depth.

The findings presented herein provide new support for the use of biomarkers (particularly %CDT) in elucidating a causal effect of heavy alcohol consumption in high BP. As such, it supports other literature that %CDT might be a useful, and cost-effective, tool to monitor heavy alcohol use in routine medical practice (Fleming and Mundt, 2004; Dillie et al., 2005). This has far reaching clinical implications, as providers may monitor the role of alcohol in hypertension using %CDT as a supplemental aid, rather than relying solely on patient report. While not an aspect of this report, future research should examine the clinical utility of using %CDT as an educational/motivational tool to get hypertensive patients to reduce, or refrain from, heavy alcohol consumption. Also, these data imply that, close to complete abstinence might be necessary to significantly lower BP in alcohol-dependent individuals. Whether this might be due to sensitization to the BP-elevating effects of alcohol or just an epiphenomenon of unreliable alcohol consumption reports needs further exploration. Finally, there is clearly a need for more sensitive and specific biomarkers of various levels of alcohol consumption. Markers that monitor for any drinking, which is important in BP elevation as suggested by our data, might be useful for feedback during the treatment of hypertension. However, markers such as ethylglucuronide that only capture drinking in the 24–48 h prior to testing (Wurst et al., 2003) limit their utility. Nevertheless, the role of biomarkers/lab tests of alcohol consumption may play an increasingly important role in the treatment of hypertension.

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REFERENCES


