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14. ABSTRACT

The study is designed to evaluate the utility of levels of two phospholipids in serum as a marker of past drinking behavior across month-level time horizons, in an attempt to improve ability to measure alcohol quantity consumed and associated damage better than can be done with ethyl alcohol level measures and other existing tests that only measure very recent exposure and poorly reflect quantity consumed. This will be achieved by correlating detailed questionnaire data on alcohol consumption with serum phospholipid levels in subjects not selected for alcohol abuse (part I) and subjects under alcohol abuse treatment (part II). The Department of Defense-funded study will conduct Part I at the VA hospital and Part II at the Fairbanks treatment facility. Part I involves a single study session (n=280), while Part II will involve serial blood draws and phospholipid measures at several treatment visits (n=60). The study is open to 280 subjects for Part I, and 60 subjects for part II. Part I has 179 consented, and 18 screen fails; Part II has 33 consented (one withdrew from the study) and 8 screen fails. The study is currently active and analysis has not been completed. Since the inception of the study, we have not experienced any problems with subjects' recruitment. To date, we have recruited 197 subjects into Part I of the study and 41 subjects into part II.

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INTRODUCTION

The abuse of alcohol is a major public health problem, and the diagnosis and care of patients with alcohol abuse and dependence is hampered by the lack of tests that can detect dangerous levels of drinking or relapse during therapy. Such tests would be valuable to screen for excessive alcohol use, to monitor subjects during alcohol rehabilitation, and to monitor abstinence in subjects with alcohol-induced organ injury (such as those with alcoholic liver disease). Alcohol itself is present in blood or urine samples for only a short time after stopping drinking, and thus doesn't provide information beyond the most recent period of alcohol use. At present, we routinely check for AST/ALT, Mean Corpuscular volume (MCV), and carbohydrate deficient transferrin (CDT) for ongoing alcohol use. However, these tests do not bear a relationship to quantity of alcohol consumed, and do not become abnormal quickly when patients relapse into drinking. The goal of this study is to determine if the levels of serum phospholipids (sphingomyelin and lysophosphatidylcholine) correlate with excessive alcohol use as defined by the NIH/NIAAA. The long term goal of our proposal is to determine the diagnostic utility of phospholipids, sphingomyelin and lysophosphatidylcholine, as the potential biomarkers for excessive alcohol use (EAU).

BODY

The proposed project responds directly to the Fiscal Year 2011, Peer Reviewed Medical Research Program (PRMRP) announced by the Department of Defense; which calls for scientific research in the area of drug and alcohol use. Our proposal is to determine the diagnostic utility of phospholipids, sphingomyelin and lysophosphatidylcholine, as the potential biomarkers for excessive alcohol use (EAU). Drinking becomes excessive when it causes or elevates the risk for alcohol-related problems or complicates the management of other health problems. According to the NIH/NIAAA (**National Institute on Alcohol Abuse and Alcoholism)**, excessive drinking is defined as men who drink more than 4 standard drinks in a day (or more than 14 per week) and women who drink more than 3 drinks in a day (or more than 7 per week) (1). Non-civilian military personnel have been deployed in support of the war efforts in Afghanistan (Operation Enduring Freedom, OEF) and Iraq (Operation Iraqi Freedom, OIF) since September 11, 2001. These sustained combat operations have resulted in military personnel experiencing physical threat or actual injury during the deployment and difficult adjustments during post-deployment period (2). Negative life stress is a major contributor to the onset and exacerbation of EAU; a rising epidemic reported to be as high as 40% among returning veterans (3). The prevalence of EUA is alarming, and the vigilance and action to identify veterans with EAU is of importance. The consequences of under-detection of EAU, thus delayed intervention are serious because relative risk of alcohol-related health conditions such as alcoholic hepatitis, alcoholic cirrhosis, pancreatitis, and hepatocellular carcinoma, is increased with the amounts and duration of alcohol consumed per day (4).

Why is identifying the potential biomarkers with improved sensitivity and specificity to screen for EAU important? While detailed efforts have been made to construct interview formats that correctly quantify alcohol intake, such as Alcohol Use Disorder Identification Test Consumption (AUDIT-C)(5), CAGE (6), or including reports from collateral individuals (family and friends who interact with the subject)(7), these approaches have their limitations. This is especially true in cases where individuals are motivated to deny or minimize the magnitude of drinking behavior to mitigate personal ramifications

(8). Self-reporting mechanisms will continue to have utility in clinical and research settings; however, their use is constrained by limitations in time, resources, and training of personnel when using self report mechanisms. One study showed that most primary care physicians do not screen for alcohol problems with questionnaires during clinic visit (9). However, they often conduct a battery of clinical tests such as gamma-glutaryltransferase (GGT), mean corpuscular volume (MCV), and aspartate aminotransferase (AST). Elevation of these markers could alert physicians to possible excessive drinking, though, these tests are neither sensitive nor specific for EAU (9;10). These limitations are the basis of this proposal to identify reliable potential markers of EAU, based on our preliminary data in section C (Figures 3-5). The addition of sensitive biomarkers not only would confirm the self-report but would provide results from an objective biochemical test to help physicians to motivate patients to either stop drinking or cut back to low-risk levels.

Besides questionnaires, several laboratory tests have been used to screen for alcohol use in clinical practice. Among them are GGT, MCV, AST, alanine aminotransferase (ALT) sialylation of apolipoprotein J, carbohydrate deficient transferring (CDT), 5-hydroxytryptophol and ethyl glucuronide (11). However, we found that the ability of these markers to determine the levels of alcohol drinking revealed low sensitivities and specificities (10). It is possible that many of these commonly used markers are related to hepatic function; which is well known to be altered with EAU. Hepatic function is also impaired; however, in several conditions; which lead to false positives and reduced specificities (11). Moreover, these tests do not bear a linear relationship to the quantity of alcohol consumed, and do not become abnormal quickly when treated patients relapse into drinking (12). Taken together, new markers with good sensitivity, specificity, and ease of use are needed to screen for EAU and for monitoring of abstinence.

Metabolomics, the study of metabolites (*including lipid molecules*) is an emerging and potentially important area of basic and translational research. Altered metabolite levels (e.g. cholesterol is a marker for cardiovascular diseases and blood sugar level is a marker for diabetes) have been shown to be the hallmark of many metabolic diseases. Certain lysophospholipids have recently been recognized as important cell signaling molecules (13), and concentrations of these lipids are tightly controlled in biological systems and thus their levels may be markers of diseases. *The idea of using a lipidomic approach as a screening tool for EAU is novel and our preliminary data showed promising results that certain lipids especially sphingomyelin (SM) and lysophosphatidylcholine (LPC) might improve the sensitivity and specificity to screen for EAU.* Mechanistically, several lines of evidence suggest that alteration in serum phospholipids occurs with EAU. Alcohol activates acidic sphingomyelinase, an important enzymes involved in sphingolipid metabolism (14) and it induces fatty acid synthesis pathways which is regulated by sphingomyelinase, another form of phospholipid (15). In accordance with our study in mice fed with ethanol for 4 weeks (16), we found significant changes in the levels of serum phospholipids (especially SM and LPC) in human subjects with documented EAU, and observed the reversal trend in their levels after abstinence, suggesting that these markers, either used alone or in combination with currently available laboratory tests, might be effective to screen for EAU. We will systematically study this in detail this proposal.

KEY RESEARCH ACCOMPLISHMENTS

The study is designed to evaluate the utility levels of two phospholipids in serum as a marker of past drinking behavior across month-level time horizons, in an attempt to improve ability to

measure alcohol quantity consumed and associated damage better than can be done with ethyl alcohol level measures and other existing tests that only measure very recent exposure and poorly reflect quantity consumed. This will be achieved by correlating detailed questionnaire data on alcohol consumption with serum phospholipid levels in subjects not selected for alcohol abuse (part I) and subjects under alcohol abuse treatment (part II). The Department of Defense-funded study will conduct Part I at the VA hospital and Part II at the Fairbanks treatment facility. Part I involves a single study session (n=280), while Part II will involve serial blood draws and phospholipid measures at several treatment visits (n=60). The study is open to 280 subjects for Part I, and 60 subjects for part II. Part I has 179 consented, and 18 screen fails; Part II has 33 consented (one withdrew from the study) and 8 screen fails. The study is currently active and analysis has not been completed. Since the inception of the study, we have not experienced any problems with subjects' recruitment. To date, we have recruited 197 subjects into Part I of the study and 41 subjects into part II.

REPORTABLE OUTCOMES

There are no reportable outcomes.

CONCLUSION

Due to continuous recruitment, no analysis have been performed.

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APPENDICES

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