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Double-blind, randomized placebo-controlled clinical trial of benfotiamine for severe alcohol dependence

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ABSTRACT

Alcohol dependence is associated with severe nutritional and vitamin deficiency. Vitamin B1 (thiamine) deficiency erodes neurological pathways that may influence the ability to drink in moderation. The present study examines tolerability of supplementation using the high-potency thiamine analog, benfotiamine (BF), and BF's effects on alcohol consumption in severely affected, self-identified, alcohol dependent subjects. A randomized, double-blind, placebo-controlled trial was conducted on 120 non-treatment seeking, actively drinking, alcohol dependent men and women volunteers (mean age = 47 years) from the Kansas City area who met DSM-IV-TR criteria for current alcohol dependence. Subjects were randomized to receive 600 mg benfotiamine or placebo (PL) once daily by mouth for 24 weeks with 6 follow-up assessments scheduled at 4 week intervals. Side effects and daily alcohol consumption were recorded. Seventy (58%) subjects completed 24 weeks of study ($N = 21$ women; $N = 49$ men) with overall completion rates of 55% ($N = 33$) for PL and 63% ($N = 37$) for BF groups. No significant adverse events were noted and alcohol consumption decreased significantly for both treatment groups. Alcohol consumption decreased from baseline levels for 9 of 10 BF treated women after 1 month of treatment compared with 2 of 11 on PL. Reductions in total alcohol consumption over 6 months were significantly greater for BF treated women (BF: $N = 10$, -611 ± 380 standard drinks; PL: $N = 11$, -159 ± 562 standard drinks, p-value = 0.02). BF supplementation of actively drinking alcohol dependent men and women was well-tolerated and may discourage alcohol consumption among women. The results do support expanded studies of BF treatment in alcoholism.

1. Introduction

Chronic alcoholic drinking is commonly associated with serious nutritional and vitamin deficiency (Green, 1983; Hoyumpa, 1980; Laureno, 2012; Lieber, 2003; Thomson, 2000; Thomson et al., 2012; World et al., 1985). The poor dietary habits of individuals suffering from severe alcoholism are often compounded by the direct effects of alcohol which actively interfere with the absorption and use of dietary nutrients (Green, 1983; Hoyumpa, 1980; Lieber, 2003; Said and Mohammed, 2006; Said, 2011; Subramanya et al., 2010; Thomson, 2000; Thomson et al., 2012; World et al., 1985). Deficiency of B vitamins is especially problematic in the context of alcoholism due to their physical properties including high water (rather than fat) solubility which limits cellular storage within the body (Hoyumpa, 1980; Said and Mohammed, 2006; Said, 2011; Subramanya et al., 2010). In addition, several B vitamins have key roles in carbohydrate metabolism and are preferentially depleted by high rates of alcohol metabolism (Singleton and Martin, 2001; Martin et al., 2003). Severe thiamine (vitamin B1) deficiency is rare but can be associated with a serious illness (beriberi) and neurological problems which can lead to significant disability and death. Neurological syndromes in alcoholics are typically manifested as a progressive loss of central and peripheral white matter believed to result mainly from alcoholism-related thiamine deficiency (He et al., 2007; Laureno, 2012; Mellion et al., 2011).

1.1. Prevalence of thiamine deficiency in alcoholism

Nationalized fortification efforts to alleviate nutritional deficiency have reduced the occurrence of acute thiamine deficiency in most western countries even in the context of alcoholism (Backstrand, 2002); but yet, deficits in circulating thiamine has been reported in 30–80% of alcoholic inpatients (Brust, 2010; Mancinelli et al., 2003; Thomson et al., 1987). Functional deficits in the activation of thiamine dependent enzymes have been reported

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in 35% of alcoholics (Butterworth et al., 1993; Herve et al., 1995; Thomson et al., 1987, 2012), and neuropathological brain lesions characteristic of thiamine deficiency have been reported in 12.5% of autopsied brain samples from alcoholics (Harper, 2006; Harper et al., 2003). Further, inherited differences in thiamine binding and utilization have been associated with an increased vulnerability toward thiamine deficiency in certain individuals which may be exacerbated by alcoholism (Blass and Gibson, 1977, 1979; Martin et al., 1993; Mukherjee et al., 1987).

Standard inpatient care for alcoholism typically incorporates nutritional support in the form of high-dose vitamin intravenous therapy which appears effective in alleviating acute symptoms of thiamine deficiency (Markowitz et al., 2000; Thomson et al., 2012). However, the duration of these interventions, typically 2–3 days, may be inadequate to restore functional activity of chronically down-regulated thiamine-dependent enzymes in the brain and other tissues (Thomson et al., 2012). In addition, the efficacy of subsequent follow-up care which currently relies upon traditional, water-soluble, oral thiamine supplements is limited by alcoholism-related impairments in thiamine absorption and activation (Baker and Frank, 1976; Thomson et al., 2012). In light of these factors, a need exists for an effective adjuvant therapy capable of producing a sustained elevation of blood thiamine in outpatient settings, particularly in the presence of continued alcohol abuse by the patient.

1.2. Alternative thiamine analogs

Benfotiamine (BF) is a synthetic thiamine analog in a class of natural products referred to as allithiamines (Anonymous, 2006). Allithiamines are lipid-soluble molecules that are produced by plants from the *Allium* genus, in the garlic family (Lonsdale, 2004). These compounds are widely recognized for their ability to dramatically increase the bioavailability of thiamine pyrophosphate (TPP), in the blood, cerebrospinal fluid and urine (Fujiwara, 1976; Loew, 1996). First discovered in Japan in the 1950s, BF was patented for use in the United States in 1962 but was never marketed. The supplement has been widely used in Japan and Europe for decades where it is well-tolerated with no reports of serious adverse events (Anonymous, 2006). BF was licensed for use in Germany for the treatment of sciatica nerve pain in 1993. As a synthetic compound, rather than an extract, BF supplements can be purchased in a pure form.

BF is a lipid-soluble provitamin and rapidly converted to thiamine pyrophosphate (TPP) in the body (Bitsch et al., 1991). Studies of BF pharmacodynamics have confirmed its ability to elevate TPP bioavailability and to dramatically increase the activity of thiamine-dependent enzymes in alcoholics with thiamine deficiency (Bitsch et al., 1991; Greb and Bitsch, 1998; Loew, 1996; Schreeb et al., 1997). BF supplementation has been reported to increase erythrocyte transketolase enzyme activity by 3 to 4 fold compared to maximal increases of 25% reported for traditional, water-soluble, supplements of thiamine hydrochloride (Baker and Frank, 1976; Greb and Bitsch, 1998). Clinical trials with BF supplementation in Europe have identified significant improvements in the symptoms of alcoholic and diabetic neuropathy with little to no adverse effects (Anonymous, 2006; Ayazpoor, 2001; Babaei-Jadidi et al., 2003; Haupt et al., 2005; Simeonov et al., 1997; Stracke et al., 1996, 2001; Woelk et al., 1998).

1.3. Thiamine deficiency and alcohol consumption

Research in animal models have suggested that deficiency of certain B vitamins, particularly thiamine deficiency, in acute alcoholism may contribute directly to pathological drinking (Brady and Westerfeld, 1947; Eriksson et al., 1980; Impeduglia et al., 1987; Mardones, 1951, 1954, 1960; Mardones et al., 1953; Pekkanen, 1979, 1980; Pekkanen et al., 1978; Pekkanen and Rusi, 1979; Zimatkin and Zimatkina, 1996; Zimatkina et al., 2000). Rats exposed to dietary thiamine depletion or treatment with thiamine antagonists show increased total alcohol consumption that was readily reversed after thiamine rescue (Brady and Westerfeld, 1947; Eriksson et al., 1980; Impeduglia et al., 1987; Pekkanen, 1979, 1980; Pekkanen et al., 1978; Zimatkin and Zimatkina, 1996). The findings of these early studies with rats suggest subclinical levels of thiamine deficiency moderate alcohol consumption and that restoration of thiamine blood levels could help to normalize drinking behaviors.

We hypothesize that improvements in central neurological functioning in response to BF treatment will correlate with improved cognitive functioning and enhanced behavioral control which may reduce alcohol consumption- similar to effects observed in animal models and enhance recovery from alcoholism. Here, we examined the dose tolerability and effect of thiamine replacement with the high potency thiamine analog, BF, on alcohol consumption in a group of severely alcohol dependent subjects in a double-blind randomized placebo-controlled clinical trial.

2. Methods

2.1. Participants

Study participants included 120 adult men and women with a mean age of 47.5 ± 7.9 years (range: 21–59 years) who met DSM-IV-TR (American Psychiatric Association, 2000) criteria for a current Alcohol Use Disorder according to a structured interview administered by an experienced trained psychiatric nurse. Eligible subjects defined alcohol as their primary substance of abuse that was active within the previous 30 days. Intellectually impaired and seriously medically ill subjects were excluded but other comorbid psychiatric and medical illnesses were permitted. Formal inclusion and exclusion criteria were as follows.

Inclusion criteria was: DSM-IV-TR criteria for an Alcohol Use Disorder; active alcohol use or <30 days of abstinence from alcohol; age 18–60 years with a local address; ability to read and understand English. Exlusion criteria was: individuals failing to meet DSM-IV-TR diagnostic criteria for an Alcohol Use Disorder; abstinence for >30 days; age <18 or >60 years; intellectual disability or serious physical illness.

2.2. Recruitment and screening

This study was conducted under the authority of the University of Kansas Medical Center Office of Research Compliance who reviewed the study protocol and monitored study activities to ensure that appropriate steps were taken to protect the rights and welfare of humans participating as research subjects. Participants were recruited by advertisement in a local newspaper and word of mouth from the Greater Kansas City Metropolitan area between August 2008 and August 2011. Subjects were remunerated for study participation earning up to $245 for compliance with all elements of the study. Subjects were referred to an outpatient clinic and a 12-step program but no formal alcoholism treatment was offered. Subjects were not recruited from treatment programs, required to seek treatment or make a special effort to abstain from alcohol in order to participate. An initial phone screening interview of potential subjects was conducted to assess eligibility prior to enrollment.

2.3. Study design

The study was a randomized, double-blind, placebo-controlled clinical pilot. Eligible and consenting subjects were randomized

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