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Vaccine for cocaine dependence: A randomized double-blind placebo-controlled efficacy trial

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ABSTRACT

Aims: We evaluated the immunogenicity, efficacy, and safety of succinylnorcocaine conjugated to cholera toxin B protein as a vaccine for cocaine dependence.
Methods: This 6-site, 24 week Phase III randomized double-blind placebo-controlled trial assessed efficacy during weeks 8 to 16. We measured urine cocaine metabolites thrice weekly as the main outcome.
Results: The 300 subjects (76% male, 72% African–American, mean age 46 years) had smoked cocaine on average for 13 days monthly at baseline. We hypothesized that retention might be better and positive urines lower for subjects with anti-cocaine IgG levels of ≥42 μg/mL (high IgG), which was attained by 67% of the 130 vaccine subjects receiving five vaccinations. Almost 3-times fewer high than low IgG subjects dropped out (7% vs 20%). Although for the full 16 weeks cocaine positive urine rates showed no significant difference between the three groups (placebo, high, low IgG), after week 8, more vaccinated than placebo subjects attained abstinence for at least two weeks of the trial (24% vs 18%), and the high IgG group had the most cocaine-free urines for the last 2 weeks of treatment (OR = 3.02), but neither were significant. Injection site reactions of induration and tenderness differed between placebo and active vaccine, and the 29 serious adverse events did not lead to treatment related withdrawals, or deaths.
Conclusions: The vaccine was safe, but it only partially replicated the efficacy found in the previous study based on retention and attaining abstinence.

1. Introduction

Stimulant use disorders remain a significant public health concern (SAMHSA, 2012). For example, cocaine was noted more often than any other illicit drug among emergency department visits in the United States (SAMHSA, 2013). Currently, there are no medications that have regulatory approval for cocaine addiction leading to an urgent need for novel therapeutic approaches. TA-CD is a vaccine being developed for the treatment of cocaine dependence. Cocaine is a molecule that, by itself, is too small to elicit an antibody response. However, conjugation to larger, immunogenic protein carriers can enable production of antibodies specific to small molecules. The B subunit of cholera toxin (CTB) is a highly immunogenic protein known to elicit a potent antibody response. TA-CD vaccine is designed to induce formation of anti-cocaine antibodies. This cocaine vaccine covalently links succinylnorcocaine (SNC) to cholera toxin B (rCTB), which has a worldwide safety record for cholera immunization (Jertborn et al., 1992, 1994; Holmgren et al., 1994; Svennerholm et al., 1984). The anti-drug antibodies elicited by TA-CD bind to cocaine entering the bloodstream, forming antigen-antibody complexes too large to cross the

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blood-brain barrier. In sufficient quantity and appropriate affinity, such antibodies can therefore prevent high concentrations of cocaine from reaching the mid-brain. The absence of reward stimulus in the brain should reduce the reinforcing psychoactive effects of cocaine. By blocking the pleasurable response to cocaine, it is expected that cocaine usage could be reduced in subjects undergoing treatment for cocaine dependence.

The concentration of anti-cocaine antibody in the blood must be sufficient to bind a significant amount of the drug in order to be effective. The peak plasma amount of cocaine that users need to experience pleasure in human laboratory studies is approximately 0.5 μM (Jenkins et al., 2002), and to bind 90% of this amount of cocaine requires approximately 42 μg/ml of moderately high affinity antibody (Fox et al., 1996; Fox, 1997; Orson et al., 2007). We therefore compared reductions in cocaine use for the placebo group to two groups of vaccinated subjects: those with peak IgG antibody levels above (high IgG) versus below (low IgG) 42 μg/ml IgG. We also know from previous work that the window of optimal IgG levels would be after week 8 and that after week 16 these IgG levels would fall. (Kosten et al., 2002; Martell et al., 2005, 2009). Thus, we hypothesized that subjects with high IgG levels above 42 μg/ml should have more cocaine-free urines, more sustained abstinence (>2 weeks) and greater treatment retention than the subjects getting placebo or having low IgG responses to the vaccine.

2. Methods

2.1. Site and population

We recruited cocaine dependent subjects (DSM IV-TR criteria; American Psychiatric Association, 1994) into outpatient clinical programs at six sites: Baylor/Houston MED VAMC, Columbia University, Johns Hopkins, New York University, University of Pennsylvania and University of Cincinnati. This study followed Good Clinical Practices, and subjects signed informed consents that included financial inducements for study retention and were approved by the institutional review boards of each participating institution.

2.2. Participants

Between October, 2010 and March, 2012 we randomized 300 of 736 screened cocaine dependent men and women who had cocaine metabolites in their urine and were aged 18 to 55. Fig. 1 summarizes subject recruitment, screening exclusions and retention. Subjects were excluded primarily for lack of cocaine positive urines during screening, for no motivation to stop using cocaine or for major medical or psychiatric illness, current infection, psychotropic or corticosteroid medications, or a history of other vaccinations or blood product use within 30 days. Female participants had to be on birth control or be incapable of child bearing. Complete medical examinations included routine blood testing and an electrocardiogram.

2.3. Interventions

Vaccination. The TA-CD vaccine is succinylnorcocaine covalently linked to cholera toxin B (SNC-rCTB) that is adsorbed onto aluminum hydroxide adjuvant. The placebo contained saline and aluminum hydroxide. Subjects were randomized to five 0.5 ml intramuscular vaccinations of 400 micrograms of active (SNC-rCTB) or placebo vaccine at weeks 1, 3, 5, 9, and 13 (Kosten et al., 2002; Martell et al., 2009).

Randomization. Subjects were randomized equally to each treatment and all subjects were analyzed. Randomization assignments were securely stored centrally, and research staff, investigators, and

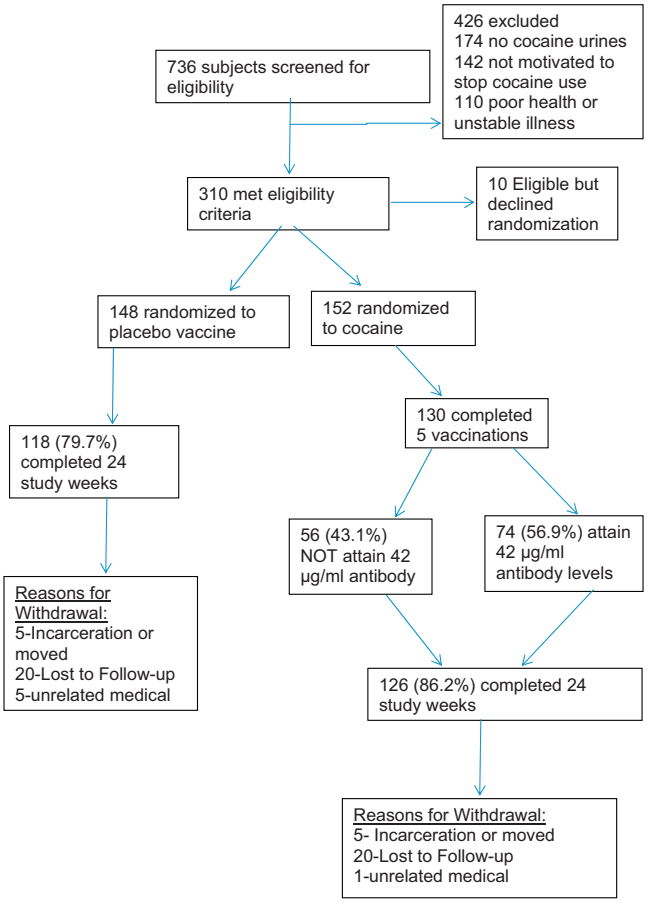

Fig. 1. Flow chart of study participants screened, randomized and completing study according to CONSORT guidelines.

subjects were blinded until the database was unlocked in January 2013.

Counseling. Masters level substance abuse counselors provided optional individual cognitive behavioral therapy (CBT) sessions for 30–45 min (SAMHSA, Treatment Improvement Protocol 33, 2010). The patients participated in an average of 11.2 (SD 4.4) out of 16 therapy sessions with no difference between the active and placebo groups.

2.4. Safety monitoring

Medical staff evaluated the vaccination site for erythema, induration, and/or tenderness after injection and monitored subjects for general health and subjective adverse events. Hematology and clinical chemistries were drawn at baseline and weeks 12, 16 and 24. Medical interventions or medications started after vaccination were considered possible adverse events (AE) and along with reasons for study termination were tabulated by treatment group.

2.5. Objectives

The overall goal of the study was to compare the effect of TA-CD to placebo on the degree of modulation of cocaine use in cocaine-dependent individuals (DSM-IV-TR) who are motivated to quit or reduce use of cocaine. The primary objective of this study is to evaluate the effect of 5 doses of TA-CD 400 μg compared to placebo on cocaine use over 8 weeks (Weeks 9 to 16 inclusive).

Secondary objectives included evaluating the safety and tolerability of vaccination through the week 24 study follow-up.

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