ORIGINAL ARTICLE

Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients

A Randomized, Double-blind, Placebo-Controlled Efficacy Trial

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Context: Cocaine dependence, which affects 2.5 million Americans annually, has no US Food and Drug Administration–approved pharmacotherapy.

Objectives: To evaluate the immunogenicity, safety, and efficacy of a novel cocaine vaccine to treat cocaine dependence.

Design: A 24-week, phase 2b, randomized, double-blind, placebo-controlled trial with efficacy assessed during weeks 8 to 20 and follow-up to week 24.

Setting: Cocaine- and opioid-dependent persons recruited from October 2003 to April 2005 from greater New Haven, Connecticut.

Participants: One hundred fifteen methadone-maintained subjects (67% male, 87% white, aged 18-46 years) were randomized to vaccine or placebo, and 94 subjects (82%) completed the trial. Most smoked crack cocaine along with using marijuana (18%), alcohol (10%), and nonprescription opioids (44%).

Intervention: Over 12 weeks, 109 of 115 subjects received 5 vaccinations of placebo or succinylnorcocaine linked to recombinant cholera toxin B-subunit protein.

Main Outcome Measure: Semiquantitative urinary cocaine metabolite levels measured thrice weekly with a positive cutoff of 300 ng/mL.

Results: The 21 vaccinated subjects (38%) who attained serum IgG anticocaine antibody levels of 43 µg/mL or higher (ie, high IgG level) had significantly more cocaine-free urine samples than those with levels less than 43 µg/mL (ie, low IgG level) and the placebo-receiving subjects during weeks 9 to 16 (45% vs 35% cocaine-free urine samples, respectively). The proportion of subjects having a 50% reduction in cocaine use was significantly greater in the subjects with a high IgG level than in subjects with a low IgG level (53% of subjects vs 23% of subjects, respectively) (P=.048). The most common adverse effects were injection site induration and tenderness. There were no treatment-related serious adverse events, withdrawals, or deaths.

Conclusions: Attaining high (≥43 µg/mL) IgG anticocaine antibody levels was associated with significantly reduced cocaine use, but only 38% of the vaccinated subjects attained these IgG levels and they had only 2 months of adequate cocaine blockade. Thus, we need improved vaccines and boosters.

Trial Registration: clinicaltrials.gov Identifier: NCT00142857

Arch Gen Psychiatry. 2009;66(10):1116-1123

COCAINE DEPENDENCE IS common, involving 1 of every 3 drug-related emergency department visits, and has substantial social and economic effects.[1,2] In 2007, the United States had 2.5 million cocaine-dependent people and only 809 000 of them were treated.[3]

The US Food and Drug Administration has not approved any pharmacotherapies for cocaine abuse, and behavioral therapies have had a wide range of efficacies with some promise for contingency management.[4-10] Experimental animal studies, however, have suggested that high levels of anticocaine antibodies can sequester circulating cocaine[11-14] and facilitate inactivation of cocaine by naturally occurring plasma cholinesterases before the drug enters the brain.[15] In both animals and humans, reducing cocaine's entry into the brain by binding antibody reduces cocaine-induced euphoria without causing any direct psychoactive effects or drug-drug interactions associated with other pharmacotherapies.[16-18]

We tested a cocaine vaccine made by covalently linking succinylnorcocaine to recombinant cholera toxin B-subunit protein, adsorbed onto aluminum hydroxide adjuvant.[19-21] The immunogenic carrier, re-

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combinant cholera toxin B-subunit protein, has a well-established safety record worldwide when used to immunize against cholera.[19,22] In a randomized, double-blind, placebo-controlled trial involving 34 abstinent cocaine abusers engaged in outpatient treatment, we demonstrated that this vaccine was well tolerated and induced cocaine-specific IgG antibodies in a time- and dose-dependent manner.[23] No serious adverse effects occurred during 12 months of follow-up. We also showed a continued safety and immunogenicity profile in a second open-label dose-escalation study involving both cocaine-abstinent and cocaine-active users.[24] Subjective responses of the vaccinated subjects suggested that the vaccine exerted its expected reduction in euphoria during the time their antibody levels peaked, that is, between weeks 12 and 16 after the first inoculation.[23,24]

To influence drug-seeking behavior, the concentration of anticocaine antibodies in the blood must attain a target level. Early rat studies with succinylnorcocaine–cholera toxin B-subunit protein vaccine showed that 0.7 mg/mL of high-affinity IgG was sufficient to bind 8.7μM cocaine.[11] Since cocaine users can experience pleasure at peak plasma cocaine concentrations as low as approximately 0.5μM,[25] we hypothesized that the antibody would need to bind and capture this amount of cocaine to slow delivery of typically abused amounts into the brain. Considering the 2 binding sites on each antibody, we calculated needing 0.28μM moderate-affinity anticocaine antibodies in the blood, which equals our target of 43 μg/mL of specific IgG for subanalyses of efficacy.[11,12,26]

We also hypothesized distinct patterns of cocaine use based on subjects' antibody levels. We have previously shown that 25% to 30% of vaccinated subjects produce relatively low antibody levels.[23,24] Furthermore, we knew that IgG antibody levels would reach a maximum between weeks 12 and 16, after which IgG antibody levels would begin to fall. Thus, we postulated that starting during week 9, immunized volunteers who made 43 μg/mL or more of anticocaine antibodies would use less cocaine than those who received the placebo or those who made less than 43 μg/mL following this series of vaccinations.

METHODS

SITE AND POPULATION

Participants meeting *DSM-IV* criteria[27] for cocaine and opioid dependence were enrolled in an outpatient methadone maintenance treatment program in West Haven, Connecticut. We studied methadone-maintained subjects because retention in methadone maintenance programs is substantially better than in primary cocaine treatment programs[28] and we needed to retain these volunteers for 12 weeks to complete the vaccination series. We also offered subjects $15 per week to enhance retention. This study was conducted in accordance with Good Clinical Practices and was approved by the institutional review boards of the Veterans Affairs Connecticut Healthcare System and Yale University School of Medicine. All subjects spoke and understood English and gave written informed consent.

PARTICIPANTS

Between October 2003 and April 2005, 115 of 122 screened subjects were enrolled and randomized. **Figure 1** summarizes subject recruitment and retention. Subjects were excluded for major medical or psychiatric illness, ongoing infection or fever, use of any prescribed psychotropic medications, receipt of blood products within 3 months of screening, or a history of other vaccinations or corticosteroid use within 30 days. No subjects were transferred from methadone maintenance, but 30 patients had previous methadone maintenance treatment. Eligibility included men or women aged 18 to 55 years who met *DSM-IV* criteria for cocaine and opioid dependence, had urine samples positive for cocaine, and did not have a clinically unstable chronic disease. Enrolled women had to be nonchildbearing or willing to use birth control. Race was self-reported at screening to determine whether sufficient numbers would allow ethnic subanalyses. Complete medical and psychiatric examinations were performed; additional assessments included electrocardiography, urine toxicology for illicit substances, and blood work including human immunodeficiency virus testing. We retained 94 of 115 subjects (82%) during the 24 weeks, with equivalent retention in placebo and vaccinated groups (Figure 1).

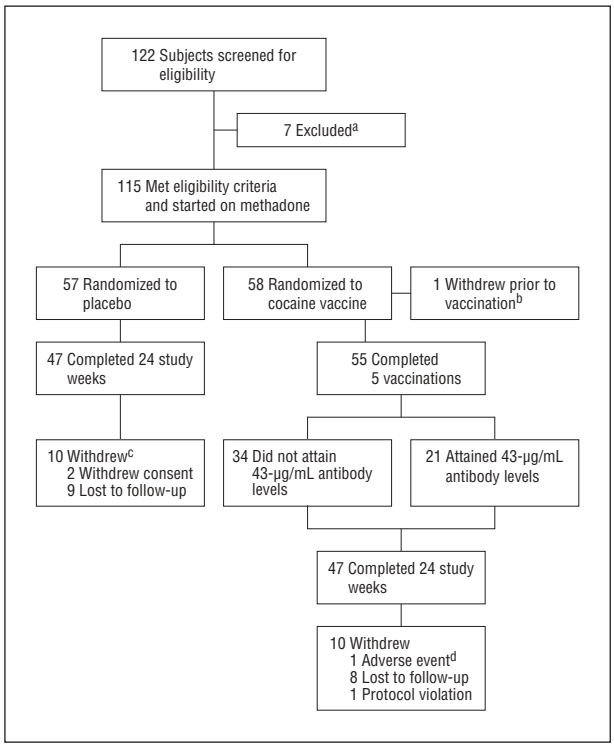

Figure 1. Flowchart of study participants. [a]Did not meet inclusion criteria (described in study eligibility). [b]Incarceration. [c]One subject had more than 1 reason for withdrawal. [d]New diagnosis of ankylosing spondylitis.

INTERVENTIONS

Vaccination

The vaccine was made by linking succinylnorcocaine covalently to recombinant cholera toxin B-subunit protein. This conjugate was then adsorbed onto aluminum hydroxide adjuvant. The placebo contained saline and aluminum hydroxide. Subjects were randomized to receive either 5 vaccinations of 360 μg of active vaccine (succinylnorcocaine–recombinant cholera toxin B-subunit protein) or placebo as 0.5-mL intramuscular deltoid injections at weeks 0, 2, 4, 8, and 12. Efficacy assessment began at week 8, when most vaccine responders should have significant IgG anticocaine antibody levels.[23,24]

Methadone Maintenance

Subjects were maintained according to the manufacturer's and Connecticut's standard methadone induction and maintenance procedures[29] (Roxane Laboratories, Columbus, Ohio; Mallinckrodt Pharmaceuticals, St Louis, Missouri[30]). Methadone maintenance therapy was initiated 2 weeks prior to the first vaccination, and doses stabilized by week 8 of the study at a mean (SD) stabilization dose of 83 (16) mg daily. At week 21, subjects were offered either a scheduled detoxification or transfer to another methadone treatment program. If detoxified, subjects were tapered on their methadone dose over a 6-week period (weeks 21-26). If transferred, they remained on methadone through week 24 of the study and then transferred. Fifteen of the 114 patients chose the 6-week detoxification.

Counseling

All subjects participated in individual, weekly, 30- to 45-minute cognitive behavioral relapse-prevention therapy sessions conducted by trained substance abuse counselors.[31] During these counseling sessions, urine toxicology results were reviewed with the subjects.

SAFETY MONITORING

Medical staff evaluated the vaccination site for erythema, induration, and/or tenderness at 1, 2, and 48 hours after injection. Subjects were monitored daily for both general health and subjective adverse events (AEs). Safety laboratory analyses that included hematology and clinical chemistries were performed at baseline, at 2-week intervals through week 12, and at 16 and 24 weeks. Serious and nonserious AEs possibly related to the vaccine were defined as any new illness or exacerbation of a preexisting condition occurring after the start of the vaccination series. Medications taken or medical interventions performed after vaccination were evaluated as possible AEs. Serious and nonserious AEs and reasons for study termination were tabulated by treatment group.

OBJECTIVES

The primary objective was to evaluate the efficacy of the vaccine vs placebo in reducing cocaine use. Secondary objectives included confirming vaccine immunogenicity through IgG anticocaine antibody levels and evaluating the safety and tolerability of the vaccination through a 20-week study period and at a 24-week follow-up. We also analyzed the relationship between IgG anticocaine antibody levels and the use of cocaine as determined by serial thrice-weekly urine samples for cocaine metabolites.

OUTCOME MEASURES

Efficacy Analysis

To compare the numbers of cocaine-free urine samples each week between vaccinated and placebo-receiving subjects, we used intent-to-treat analysis over 2 intervals: one up to week 16 and a second through week 20. This first interval to week 16 corresponds to the time when antibody levels were expected to peak; antibody levels would then decline from weeks 16 to 20. We used a repeated-measures assessment (random regression model) to estimate the effect of treatment on the frequency of cocaine-free urine samples in all subjects during the 16- and 20-week study periods. Only 4% of urine samples were missing owing to treatment dropouts; an additional 5% of samples were not collected because of missed visits or other reasons during the study.

Exploratory Efficacy Analysis

We compared the weekly rate of cocaine-free urine samples for placebo control subjects and 2 groups of actively vaccinated subjects, who were divided into groups with high and low IgG levels using a peak-level cutoff of 43 μg/mL of IgG anticocaine antibodies. We also compared the number of subjects who were cocaine-free in at least half of their urine samples between weeks 8 and 20 among the groups with high vs low IgG levels. We separately analyzed the 45 vaccinated subjects remaining after excluding 3 who dropped out before week 15 and 7 who did not use cocaine during weeks 8 to 20 since anticocaine antibodies could not have affected their cocaine use.[32,33]

Quantitative Antibody Measurement

Serum IgG anticocaine antibody levels were measured by an enzyme-linked immunosorbent assay. The antigenic target was cocaine conjugated to bovine serum albumin. Human IgG bound to this antigen was detected with a horseradish peroxidase–conjugated second antibody and an appropriate substrate.[23] Nonspecific antibody binding to the carrier alone was subtracted, and each enzyme-linked immunosorbent assay plate included wells with serially diluted polyclonal human IgG to provide an internal standard. The specificity and reproducibility of this enzyme-linked immunosorbent assay were validated using serial dilutions of a humanized monoclonal antibody to cocaine, 2E2 (Andrew Norman, PhD, Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio).[34]

Cocaine Metabolites in Urine

Urine was qualitatively tested for benzoylecgonine (BE) at the time of screening, at methadone initiation, and thrice weekly for the duration of the study. Urine BE values of at least 300 ng/mL were considered positive. A pharmacokinetic study in mice has shown that introduction of anticocaine antibodies into the circulation did not change BE excretion despite 15% cross-reactivity.[14]

Furthermore, quantitative urine BE analysis was available during weeks 8 to 20, allowing us to use the criteria by Preston et al[35] for assessing new uses of cocaine. Briefly, the criteria by Preston and colleagues separate new uses of cocaine from carryover of high BE levels by considering BE levels that are above the 300-ng/mL cutoff but are 50% or greater reductions from the urine toxicology performed 2 to 3 days earlier as indicating no new use of cocaine since the last urine testing. Thus, dropping from 1000 ng/mL of BE on Monday to 400 ng/mL on Wednesday would indicate no new use of cocaine rather than another cocaine-positive urine sample on Wednesday. We conducted appropriate subanalyses of vaccine efficacy using this strategy, but we also noted that when positive, urine BE levels were typically greater than 10 000 ng/mL. Since this value is at least 30-fold higher than the cutoff for a positive quantitative urine test result, we were further assured that we did not have false-negative urine test results in the vaccinated group due to reduced BE urinary clearance from antibody binding. Studies in experimental animals have also shown that antibody binding of cocaine in vivo does not delay cocaine clearance, reducing the risk of late false-positive test results.[14]

RANDOMIZATION

Subjects were randomized equally to each treatment and all subjects were analyzed. Randomization assignments were se-

curely stored by a pharmacist who was unblinded to treatment arms, but research staff, investigators, and subjects were blinded until the database was unlocked in June 2006.

STATISTICAL ANALYSES

Subject Demographics and AEs

Vaccine and placebo groups were compared using *t* test or the nonparametric Mann-Whitney *U* test depending on data normality, and categorical differences were compared using χ^2 or Fisher exact tests.

Vaccine Efficacy

Vaccine efficacy was tested by hierarchical linear modeling (HLM) to compare each subject's fraction of weekly urine samples free of cocaine metabolites.[36,37] The HLM method for modeling repeated measures allows for unbalanced designs with missing data, intrasubject serial correlation, and unequal variance and covariance structures over time.[36,37] These analyses were conducted using MIXOR version 2 (Donald Hedeker, PhD, and Robert D. Gibbons, PhD, University of Illinois at Chicago), a program that can implement HLM analyses with ordinal outcome data. These HLM MIXOR analyses produce logit estimates (odds ratios) in a manner similar to logistic regression and statistical significance is given as a *Z* value, which is independent of degrees of freedom.

Sample Size Estimate

Based on previous cocaine pharmacotherapy studies, we postulated that cocaine use would decrease by about 25% in the placebo group and 50% in vaccinated subjects.[38] Therefore, to attain a statistical power of 0.8 with $\alpha = .05$, it was anticipated that 60 subjects needed to enroll in each treatment arm. Because the current trial retained more than 80% rather than 50% of subjects at 6 months, fewer subjects needed to enroll and 115 rather than 120 subjects were randomized.

RESULTS

BASELINE CHARACTERISTICS, RETENTION, AND OPIOID USE

The vaccinated and placebo-receiving subjects were comparable in age, sex, and ethnicity but most subjects were white, preventing ethnic subanalysis. Most subjects (89%) considered smoked cocaine their second drug of choice after opioids, including prescription opioids. We found no statistically significant baseline demographic or drug use differences between groups, and treatment retention showed no difference; 94 subjects (82%) completed 24 weeks (**Table 1** and Figure 1). The full sample of 114 patients showed a significant increase in opioid-free urine samples from 55% (SEM, 5%) during the first 2 weeks of methadone maintenance to 68% during week 8 onward while receiving a mean stabilization methadone dosage of 83 mg daily ($F_{1,108} = 9.9$; $P = .002$). The 2 treatment groups showed no difference in opioid-free urine samples or methadone dosage.

COCAINE VACCINE–SPECIFIC IgG LEVELS

Of the 58 subjects randomized to receive active vaccine, 55 completed the series of 5 vaccinations and 54 of those 55 subjects (98%) made detectable antibody levels. **Figure 2** shows individual serum IgG anticocaine antibody levels through week 24. Notably, early antibody responders made antibodies as early as week 2; however, many subjects mounted antibody responses only after week 6. One subject had preexisting high levels of IgG anticocaine antibodies and maintained them throughout the study. Of those vaccinated, 21 (38%) attained antibody levels of 43 µg/mL or greater (group with high IgG levels), whereas 34 (62%) had levels below this threshold (group with low IgG levels), including 1 subject who made no antibodies. Only 2 subjects mounted antibody

Table 1. Baseline Clinical Characteristics of 114 Participants

Characteristic	Cocaine Vaccine (n=57)	Placebo (n=57)
Age, mean (SD), y[a]	35.6 (8.9)	36.2 (9.3)
Race/ethnicity, No. (%)[a,b]		
White	53 (93)	46 (81)
African American	2 (4)	8 (14)
Mixed	2 (4)	3 (5)
Sex, No. (%)[a]		
Male	35 (61)	41 (72)
Female	22 (39)	16 (28)
Employed, No. (%)[a]	31 (54)	33 (58)
Family history of substance use, No. (%)[a]	19 (33)	25 (44)
Cocaine history		
Age at first use, mean (SD), y[a]	22.1 (7.8)	20.9 (6.1)
Use, mean (SD), d/wk		
Before vaccine[a]	3.3 (2.9)	2.9 (2.8)
First 2 wk after vaccine[a]	2.2 (2.1)	1.9 (2.0)
Dimes used per day, mean (SD)		
Before vaccine[a]	3.5 (5.8)	2.4 (2.7)
First 2 wk after vaccine[a]	2.3 (2.1)	1.7 (1.4)
Amount spent on cocaine per day, mean, $[a]	105.00	77.00
Cocaine craving, mean (SD)[c]	3.8 (2.3)	4.2 (2.4)
Route of use, No. (%)[d]		
Intranasal	35 (61)	36 (63)
Intravenous	14 (25)	20 (35)
Smoked	46 (81)	41 (72)
Opiate history		
Age at first use, mean (SD), y	23.1 (8.1)	24.5 (12.2)
Bags of opiates used per day, No. (%)		
1-4	5 (10.4)	8 (14.5)
5-9	17 (35.4)	15 (27.3)
10-14	13 (27.1)	11 (19.3)
15-19	3 (6.3)	6 (10.9)
20-24	4 (8.3)	8 (14.5)
25-30	2 (4.2)	3 (5.4)
>30	1 (2.1)	1 (1.8)
Unknown	3 (6.3)	3 (5.4)
Other substance use, No.[d,e]		
Alcohol	8	11
Nonprescription use of opioids	27	23
Marijuana	15	20
Benzodiazepine	2	2

[a] Statistically nonsignificant ($P > .05$).
[b] Options were white, African American, Hispanic, mixed, and other.
[c] Assessed by the Cocaine Selective Severity Assessment. Maximum score is 7.
[d] Not mutually exclusive categories.
[e] By urine toxicology testing from screening (30 days prior to entry) until study completion (14 weeks).

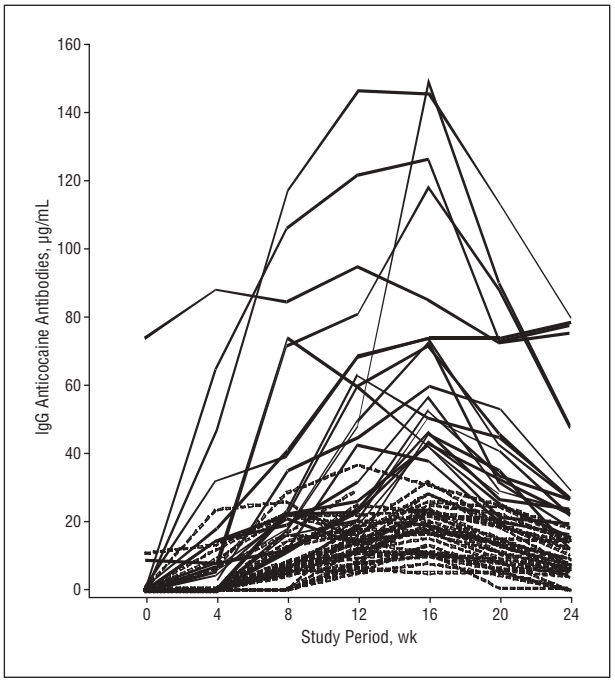

Figure 2. The IgG responses to the succinylnorcocaine–recombinant cholera toxin B-subunit protein vaccine were highly variable. Among the 55 subjects immunized with the cocaine vaccine (at weeks 0, 2, 4, 8, and 12), 21 (38%) attained levels of 43 µg/mL or greater (solid lines). Of those, 3 were highly responsive subjects, with 1 having greater than 60 µg/mL of IgG anticocaine antibodies even before immunization. Two made a vigorous response after the second injection (week 4 samples). Eight subjects made more than 43 µg/mL after 3 injections, and 8 required 4 or more injections of antigen to make a response that exceeded 43 µg/mL of IgG anticocaine antibodies. Antibody responses for the remaining 34 subjects are shown with dotted lines. The respective numbers of subjects at weeks 2, 4, 8, 12, 16, 20, and 24 were 55, 55, 55, 55, 54, 51, and 51.

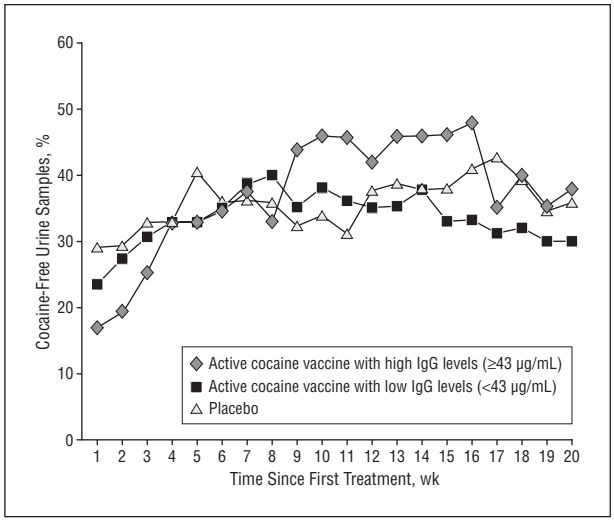

Figure 3. Mean weekly cocaine-free urine samples by medication condition for weeks 1 to 20. The y-axis represents 100 times the weekly mean proportion of cocaine-free urine samples for the 3 treatment groups. Standard errors are not shown for clarity but range from ±3% at any time. The group with high IgG levels had significantly more cocaine-free urine samples than the other 2 groups during weeks 9 to 16 (t=2.26; P=.03) and a significantly greater increase in cocaine-free urine samples than the other 2 groups from weeks 1 to 16 on hierarchical linear modeling analysis (Z=4.8; P<.001). The 3 groups did not differ in cocaine-free urine samples during weeks 17 to 20.

responses greater than 43 µg/mL before week 8, and all subjects' IgG levels declined after week 16.

COCAINE-FREE URINE SAMPLES BY TREATMENT GROUP

The frequency of cocaine-free urine samples did not differ between treatments in an intent-to-treat analysis at baseline (weeks 1-2) (33% vaccinated vs 25% placebo) (χ^2=0.3) or for the full 20 weeks. However, our HLM analyses of weekly cocaine-free urine samples for both vaccinated subjects and placebo recipients from weeks 1 through 16 showed significantly more cocaine-free urine samples as the study progressed (placebo × time interaction: Z=5.4, P<.001; vaccine × time interaction: Z=8.7, P<.001). As the difference in Z values over time suggests, the frequency of cocaine-free urine samples increased more quickly in the vaccinated group than in the placebo group (treatment × time interaction: Z=2.4, P=.01). However, after we stopped immunizing these subjects and antibody levels began to fall off during the interval between weeks 16 and 24, HLM analyses showed no significant differences in the frequency of cocaine-free urine samples between the vaccinated and placebo groups.

COCAINE-FREE URINE SAMPLES BY IgG RESPONSE TO VACCINE VS PLACEBO

Figure 3 shows the mean rates of cocaine-free urine samples in the group with high IgG levels (≥43 µg/mL) and both the placebo group and the group with low IgG levels (<43 µg/mL). Standard errors (not shown) at each time point were ±3%. From weeks 9 through 16, cocaine-free urine samples were significantly more frequent in the group with high IgG levels than in the group with low IgG levels and the placebo group (45% vs 35% cocaine-free urine samples, respectively; t_{110}=2.26; P=.03). By week 9, most of the 21 subjects with high IgG levels had antibody levels at or above 43 µg/mL; after week 16, these levels declined to those found in the subjects with low IgG levels.

Using HLM analyses of weekly cocaine-free urine samples through week 16, the group with high IgG levels and the placebo group showed significantly more cocaine-free urine samples as the study progressed (placebo × time interaction: Z=5.4, P<.001; high IgG level × time interaction: Z=9.5, P<.001), whereas the group with low IgG levels showed no significant change over time. As the difference in Z values over time suggests, the frequency of cocaine-free urine samples increased more quickly in the group with high IgG levels than in the placebo group and the group with low IgG levels (treatment × time interaction: Z=4.8, P<.001).

As a stronger test of IgG antibody levels and vaccine efficacy, we then examined the results using the 45 vaccinated subjects who remained after excluding 3 who dropped out before week 15 and 7 who did not use cocaine during weeks 8 to 20 and therefore did not directly test the vaccine's efficacy. As shown in **Figure 4**, the proportion of these subjects whose urinalyses showed no new episodes

of cocaine use at least 50% of the time (based on the criteria by Preston and colleagues) was significantly greater in the group with high IgG levels as compared with the group with low IgG levels (53% of subjects vs 23% of subjects, respectively) (Fisher exact test, $P = .048$).

ADVERSE EVENTS

Treatment-emergent or treatment-associated AEs and subject dropout related to treatment were not significantly different in vaccinated and placebo-receiving subjects (**Table 2**). Dropouts were related to incarceration and loss of housing owing to cocaine use. All of the reported AEs were considered mild or moderate in intensity. The more frequent AEs recorded for vaccinated subjects as compared with placebo recipients were as follows: injection site induration (3% vs 0%, respectively), site tenderness (10% vs 6%, respectively), feeling cold (12% vs 7%, respectively), hot flashes (19% vs 12%, respectively), hyperhydrosis (15% vs 10%, respectively), and nausea (14% vs 2%, respectively). Treatment-emergent severe AEs included a toothache and tooth abscess in 2 placebo-receiving subjects and a vaginal hemorrhage in a vaccinated subject. One vaccinated subject left owing to an exacerbation of preexisting but initially undiagnosed ankylosing spondylitis.

Six serious AEs were all deemed unrelated to the vaccine. The 3 AEs for vaccinated subjects were cocaine-related paranoia, molar pregnancy resulting in spontaneous abortion in a 42-year-old, and alcoholic pancreatitis. The 3 AEs for placebo-receiving subjects were hematuria and kidney stones, facial cellulitis, and right forearm cellulitis from self-injecting drugs.

COMMENT

We found that a cocaine-specific vaccine significantly reduced cocaine use in those cocaine-dependent subjects who attained the target antibody levels of 43 µg/mL or greater (group with high IgG levels), which animal studies indicate are elevated sufficiently to capture enough circulating cocaine to reduce its euphoric effects.[11,12,26] However, only 38% of vaccinated subjects attained these levels; these levels were not attained before week 8, and they substantially declined between weeks 16 and 24. Both the active vaccine and placebo groups reduced their cocaine use during the first 8 weeks, probably owing to reducing their illicit opiate use through methadone maintenance and cognitive behavioral therapy.[38-41] Fifty-three percent of the subjects with high IgG levels were abstinent from cocaine more than half the time as compared with only 23% of the subjects who made lesser quantities of antibody in weeks 8 to 20.

Although not statistically significant, increased use of cocaine is suggested in the group with high IgG levels after week 16 when their antibody levels began to fall relatively rapidly (Figure 3), which is typical of hapten vaccines and unlikely to be related to methadone since methadone neither enhances nor inhibits antibody responses in humans or experimental animals.[42,43] While this increased use likely reflects an effort to overcome the anticocaine antibody blockade, cocaine-related AEs (eg, overdose, hospitalization) fortunately did not increase during this interval. Optimal treatment will likely require repeated booster vaccinations to maintain appropriate antibody levels. Furthermore, efforts will be needed to retain subjects during the initial series of injections since antibody levels increased slowly over the first 3 months when patients were immunized according to the protocol used in these studies. Other treatments need to be used during this early treatment period to encourage abstinence. As an example, to retain subjects in this study during the initial slow increase in antibody responses, we enlisted cocaine-dependent subjects who were enrolled in a methadone maintenance program. Methadone-maintained pa-

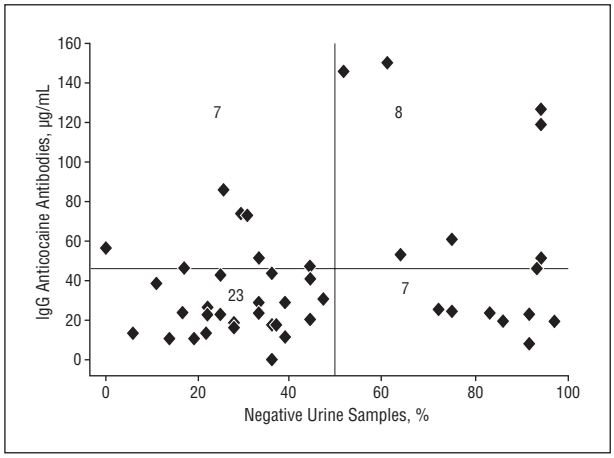

Figure 4. Scatterplot of peak antibody response by percentage of cocaine-negative urine samples. Diamonds indicate values of peak antibody response (typically at week 16) in individual vaccinated subjects plotted against their percentage of cocaine-negative urine samples using the criteria by Preston et al[35] for new uses of cocaine during weeks 8 through 20. The graph is divided into quadrants by a horizontal line at the 43-µg/mL antibody level and a vertical line at 50% cocaine-free urine samples. The numbers in each quadrant indicate the number of subjects in each quadrant. The proportion of subjects who had 50% or more cocaine-free urine samples is significantly greater in those with IgG anticocaine antibody levels of 43 µg/mL or greater than in those with lower antibody levels (Fisher exact test, $P = .048$).

Table 2. Summary of Adverse Events

AEs	Placebo (n = 57)	Cocaine Vaccine (n = 57)
Subjects with treatment-emergent AEs, No. (%)[a,b]	55 (96)	54 (95)
Subjects with treatment-associated AEs, No. (%)[a,c]	6 (10.5)	11 (19.3)
Total reports of treatment-emergent AEs, No.[b]	417	491
Total reports of treatment-associated AEs, No.[c]	9	23
Subjects discontinued owing to AEs, No. (%)[a]	0	1 (2)

Abbreviation: AEs, adverse events.
[a] Statistically nonsignificant (Fisher exact test, $P > .05$).
[b] A treatment-emergent AE was defined either as a new illness with an onset date on or after the start of the vaccination series or as exacerbation of a preexisting condition after the start of the vaccination series.
[c] A treatment-associated AE was an AE that was possibly, probably, or definitely related to the treatment by the investigator.

tients may remain longer in treatment while continuing to use cocaine than would primary cocaine-dependent patients, who would drop out. Thus, enhanced retention with methadone maintenance could have resulted in longer durations of continued cocaine use, although the baseline patterns (2-3 d/wk) and amount (2-4 dimes/use) of cocaine use (Table 1) were similar to those of primary cocaine users.[4-6,8]

This study did not achieve a significant difference in complete abstinence with immunization, and the significant reduction in cocaine use occurred in that minority of patients who attained our target antibody responses (high IgG levels). Nevertheless, it could be argued that a reduction in cocaine use rather than complete abstinence is therapeutically meaningful. More than half (53%) of the group with high IgG levels showed no new episodes of cocaine use at least 50% of the time (criteria by Preston and colleagues) and doubled their cocaine-free urine samples from a baseline lower than 20% to 45% (Figure 3). Doubling of cocaine-free urine samples has been associated with a significant improvement in social functioning as assessed by the Social Adjustment Scale in a meta-analysis of 368 subjects in two 25-week, randomized, controlled trials of behavioral abstinence reinforcement in methadone-maintained cocaine abusers, a population similar to that in our study.[44] Also, in a double-blinded, placebo-controlled human laboratory study, actively vaccinated cocaine-dependent subjects who achieved antibody levels of 22 μg/mL or greater described a 90% reduction in the effects of 50 mg of smoked cocaine as compared either with their prevaccination baseline or with subjects whose peak antibody levels were less. This result may reflect a lower dose of cocaine used in this controlled setting than in the outpatient unrestricted conditions of the current study.[45] Thus, reducing cocaine use can be therapeutically meaningful and is critically dependent on the achievement of appropriate antibody levels.

The rise and decline in IgG anticocaine antibody levels over 6 months seen in these subjects with this small-molecule conjugate vaccine are similar to the response kinetics found in studies with other recent human conjugate vaccines such as for angiotensin and nicotine.[18,46-50] While the long-lived antibody responses described in classic immunology would be desirable, the potent adjuvants (eg, Freund complete adjuvant) used in experimental animals are too toxic for humans. Using similar numbers of boosters and adjuvants as in our study, both antiangiotensin and antinicotine antibody levels declined over a few months. While it is not clear whether all cocaine abusers will benefit from persistence of high antibody levels, short-term blockade of cocaine by the vaccine is likely to have limited efficacy as does short-term opiate blockade by naltrexone hydrochloride.[18,51] Thus, the goals for future vaccine development will be to increase the proportion of subjects who can attain the desired antibody levels and to extend these periods of abstinence through long-term maintenance of these adequate antibody levels. We look forward to extending our promising findings in a broader population of cocaine abusers as we also reach for these future vaccine development goals.

Submitted for Publication: September 22, 2008; final revision received March 15, 2009; accepted March 16, 2009.
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Author Contributions: Drs Martell and Kosten had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: Dr Martell is currently employed as a medical director at Pfizer, Inc.
Funding/Support: This work was supported by grants 1 R01 DA15477, K05-DA 0454 (Dr Kosten), and P50-DA12762 from the National Institute on Drug Abuse and by the Veterans Affairs Mental Illness Research, Education, and Clinical Center (New England MIRECC). Dr Martell was provided salary support by the Veteran's Affairs Office of Research and Development/Cooperative Studies Program Career Development Award CRCD #733A at the time the research was conducted. Celtic Pharmaceuticals supplied the succinylnorcocaine–recombinant cholera toxin B-subunit vaccine and gave Dr Kosten travel fees for consultative services.
Role of the Sponsor: Celtic Pharmaceuticals had 10% involvement in the design and conduct of the study and 5% involvement in the collection, management, and interpretation of the data (involvement limited to site monitoring). Antibody levels were independently measured by a contract laboratory paid by Celtic Pharmaceuticals and by our laboratory at the Michael E. DeBakey Veterans Affairs Medical Center. Celtic Pharmaceuticals offered some comments prior to initial submission of the manuscript.
Additional Information: This work was fully approved by the Yale University Human Investigation Review Committee and the Veterans Affairs Connecticut Healthcare System institutional review board.

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