Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone Maintained Patients: A Randomized Double-Blind Placebo-Controlled Efficacy Trial

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Abstract

Context—Cocaine dependence, which affects 2.5 million Americans annually, has no FDA approved pharmacotherapy.

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

Design—24 week Phase IIb 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 2003–2005 from greater New Haven, CT.

Participants—115 methadone maintained subjects (67% male, 87% Caucasian, aged 18–46) were randomized to vaccine or placebo and 82% completed the trial. Most smoked crack cocaine along with using marijuana (18%), alcohol (10%), and non-prescription opioids (44%).

Intervention—Over 12 weeks 109/115 subjects received five vaccinations of placebo or succinylnorcocaine linked to cholera B protein.

Main Outcome Measure—Semi-quantitative urinary cocaine metabolite levels measured thrice weekly with positive cutoff of 300 ng/ml.

Results—The 38% of vaccinated subjects who attained serum IgG anti-cocaine levels $\geq$ 43 µg/mL (high IgG) had significantly more cocaine-free urines than those with < 43 µg/mL (low IgG) and the placebo subjects during weeks 9 to 16 (45% vs 35%). The proportion of subjects having a 50% reduction in cocaine use was significantly greater in the high IgG than low IgG subjects (0.53 vs.

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0.23) (P<0.04). The most common side 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 anti-cocaine antibody levels was associated with significantly reduced cocaine use, but only 38% of the vaccinated attained these IgG levels and they had only 2 months of adequate cocaine blockade. Thus, we need improved vaccines and boosters.

Introduction

Cocaine dependence is common, involving one of every three drug related emergency department visits, and has substantial social and economic impacts on those afflicted [1, 2]. In 2007 the United States had 2.5 million cocaine dependent people, and only 809,000 of them were treated [3].

The FDA 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 anti-cocaine 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 (SNC) to cholera B protein (rCTB), adsorbed onto aluminum hydroxide adjuvant. [19–21] The immunogenic carrier, rCTB, 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 out-patient 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 follow-up. We also showed a continued safety and immunogenicity profile in a second open-label dose escalation study involving both cocaine abstinent and 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 anti-cocaine antibody in the blood must attain a target level. Early rat studies with cocaine-CTB vaccine showed that 0.7 mg/ml of high affinity IgG was sufficient to bind 8.7µM of cocaine [11]. Since cocaine users can experience pleasure at peak plasma cocaine concentrations as low as approximately 0.5 µM, [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 two binding sites on each antibody, we calculated needing 0.28 µM of moderate affinity anti-cocaine antibody in the blood, which equals our target of 43 ug/ml of specific IgG for sub-analyses of efficacy [11, 12, 26].

We also hypothesized distinct patterns of cocaine usage based on subjects' antibody levels. We have previously shown that 25–30% 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 more than 43 ug/ml of anti-cocaine antibodies would use less cocaine than those immunized with the placebo or those who made less than 43 ug/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 out-patient 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 VA 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 three months of screening, or a history of other vaccinations or corticosteroid use within thirty days. None were transferred from methadone maintenance, but 30 patients had previous methadone maintenance treatment. Eligibility included men or women aged 18 to 55 who met DSM-IV criteria for cocaine and opioid dependence, had positive urine cocaine, and did not have a clinically unstable chronic disease. Enrolled women had to be non-child bearing or willing to use birth control. Race was self-reported at screening to determine whether sufficient numbers would allow ethnic sub-analyses. Complete medical and psychiatric examinations were performed; additional assessments included electrocardiogram, urine toxicology for illicit substances, and blood work including HIV testing. We retained 94 of 115 (82%) subjects during the 24 weeks with equivalent retention in placebo and vaccinated groups (Figure 1).

INTERVENTIONS

VACCINATION

The vaccine was made by linking succinylnorcocaine covalently to cholera B (SNC-rCTB). This conjugate was then adsorbed onto aluminum hydroxide adjuvant. The placebo contained saline and aluminum hydroxide. Subjects were randomized to receive either five vaccinations of 360 micrograms of active (SNC-rCTB) 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 anti-cocaine 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; PDR, 1998). Methadone maintenance therapy was initiated 2 weeks prior to the first vaccination and doses stabilized by week 8 of the study at a mean stabilization dose of 83 (SD 16) mg daily. At week 21, subjects were offered either a schedule detoxification or transfer to another methadone treatment program. If detoxified, subjects were tapered on their methadone dose over a six-week (weeks 21–26) period. If transferred, they remained on methadone through week 24 of the study and then transferred. Fifteen of the 114 patients chose the six week detoxification.

COUNSELING

All subjects participated in individual, weekly 30–45 minute cognitive behavioural relapse prevention therapy (CBT) sessions conducted by trained substance abuse counsellors[30]. During these counselling sessions urine toxicology results were reviewed with the subjects.

SAFETY MONITORING

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

OBJECTIVES

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

OUTCOME MEASURES

Efficacy Analysis—To compare the numbers of cocaine-free urines each week between vaccinated and placebo control subjects we used intent to treat analysis over two time 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, while from week 16 to 20 antibody levels would then decline. We used a repeated measures assessment (random regression model) to estimate the effect of treatment on the frequency of cocaine-free urines in all subjects during the 16 and 20 week study periods. Only 4% of urine samples were missing due to treatment dropouts; an additional 5% of samples were not collected for missed visits or other reasons during the study.

Exploratory Efficacy Analysis—We compared the weekly rate of cocaine-free urines for placebo controls and two groups of actively vaccinated subjects, who were divided into high and low IgG groups using a cutoff of 43 µg/ml anti-cocaine IgG peak levels. We also compared the high and low IgG groups on the number who had at least half of their urines cocaine-free between weeks 8 to 20, We separately analyzed the 45 vaccinated subjects left after excluding three who dropped out before week 15 and seven who did not use cocaine during weeks 8–20, since anti-cocaine antibodies could not have affected their cocaine use [31, 32].

Quantitative Antibody Measurement—Serum anti-cocaine IgG was measured by an Enzyme-Linked ImmunoSorbent Assay (ELISA). The antigenic target was cocaine conjugated to bovine serum albumin (BSA). Human IgG bound to this antigen was detected with horseradish peroxidase conjugated second antibody and appropriate substrate [23]. Nonspecific antibody binding to the carrier alone was subtracted, and each ELISA plate included wells with serially diluted polyclonal human IgG to provide an internal standard. This ELISA's specificity and reproducibility was validated using serial dilutions of a humanized monoclonal antibody to cocaine, 2E2, from Dr. Andrew Norman at the University of Cincinnati [33]

Urine Cocaine Metabolites—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 anti-cocaine antibodies into the circulation did not change BE excretion, despite 15% cross-reactivity [14]

Furthermore, quantitative urine BE was available during weeks 8 to 20 allowing us to use the Preston criteria for assessing new uses of cocaine.[34] Briefly, Preston criteria separate new uses of cocaine from carry-over of high BE levels by considering BE levels that are above the 300 ng/ml cut-off but are 50% or greater reductions from the urine toxicology taken 2–3 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 on Wednesday. We conducted appropriate sub-analyses of vaccine efficacy using this strategy, but we also noted that, when positive, urine BE levels were typically > 10,000 ng/ml. Since this value is at least 30-fold higher than the cutoff for a positive quantitative urine test, we were further reassured that we did not have false negative urine tests 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 tests[14].

RANDOMIZATION

Subjects were randomized equally to each treatment and all subjects were analyzed. Randomization assignments were securely stored by the pharmacist, who was un-blinded to treatment arms, but research staff, investigators, and subjects were blinded until the database was unlocked in June 2006.

STATISTICAL ANALYSES

Subject Demographics and Adverse Events—Vaccine and placebo groups were compared using Student's t-test or the non-parametric Mann Whitney U test, depending on data normality, and categorical differences were compared using chi-square 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 [35, 36]. The HLM method for modeling repeated measures allows for unbalanced designs with missing data, intra-subject serial correlation, and unequal variance and covariance structures over time[35, 36]. These analyses were conducted using MIXOR, a program which 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 [37]. Therefore, to attain a statistical power of 0.8 with an alpha of 0.05, it was anticipated that 60 subjects needed to enroll in each treatment arm. Because the current trial retained over 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 vaccine and placebo subjects were comparable in age, gender and ethnicity, but most were white preventing ethnic sub-analysis. 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; 82% completed 24 weeks (Table 1 and Figure 1). The full sample of 114 patients showed a significant increase in opioid-free urines from 55% (SEM 0.05) during the first two weeks on methadone maintenance to 68% during week 8 onward on a mean stabilization methadone dose of 83 mg daily (F= 9.9; df = 2,108; P<0.002). The two treatment groups showed no difference in opioid-free urines or methadone dose.

Cocaine Vaccine Specific IgG Levels

Of the 58 subjects randomized to receive active vaccine, 55 completed the series of five vaccinations and 98% (54/55) made detectable antibody levels. Figure 2 shows individual serum IgG anti-cocaine levels through week 24. Notably, early antibody responders made antibodies as early as week 2; however, many mounted antibody responses only after week 6. One subject had pre-existing high levels of IgG anti-cocaine antibody and maintained them throughout the study. Of those vaccinated, 21 (38%- high IgG group) attained antibody levels greater than 43 µg/ml, whereas, 34 (62%- low IgG group) had levels below this threshold, including one subject who made no antibodies. Only two subjects mounted antibody responses > 43 ug/ml before week 8, and all subjects' IgG levels declined after week 16.

Cocaine-Free Urines by Treatment Group

The frequency of cocaine-free urines did not differ between treatments in an intention to treat analysis at baseline (weeks 1 to 2) (33% vaccinated vs. 25% placebo) (χ2=0.3) or for the full 20 weeks. However, our HLM analyses of weekly cocaine-free urines for both vaccinated and placebo recipients from weeks 1 through 16 showed significantly more cocaine-free urines as the study progressed (placebo by time: Z=5.4, p<0.001; vaccine by time: Z=8.7, p<0.001). As the difference in Z values over time suggest, the frequency of cocaine-free urines rose faster in the vaccinated than placebo group (treatment by time interaction: Z=2.45, p<0.01). 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 urines between the vaccinated and placebo groups.

Cocaine-Free Urines by IgG Response to Vaccine versus Placebo

Figure 3 shows the mean rates of cocaine-free urines in the high IgG group (>43µg/ml) and both the placebo and low IgG groups (≤43µg/ml). Standard errors (not shown) at each time point were +/− 3%. Between weeks 9 through 16 cocaine-free urines were significantly greater in the High IgG than the Low IgG and Placebo groups (45% vs 35%; t=2.26; df=110; P<0.03). By week 9 most of the 21 high IgG subjects had antibody levels at or above 43 ug/ml and after week 16 these levels declined to levels found in the low IgG subjects.

Using HLM analyses of weekly cocaine-free urines through week 16, the high IgG and placebo groups showed significantly more cocaine-free urines as the study progressed (placebo by time: Z=5.4, p<0.001; high IgG by time: Z=9.5, p<0.001), while the low IgG group showed no significant change over time. As the difference in Z values over time suggest, the frequency of cocaine-free urines increased faster in the high IgG group than the placebo and low IgG groups (treatment by time interaction: Z=4.8, p<0.01).

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 three who dropped out before week 15 and seven who did not use cocaine during weeks 8–20 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 Preston criteria) was significantly greater in the high IgG as compared to the low IgG subjects (0.53 vs. 0.23) (Fishers test, P<0.04).

Adverse Events (AE)

Treatment emergent or associated AEs and subject dropout related to treatment were not significantly different in vaccinated and placebo subjects (Table 2). Dropouts were related to incarceration and loss of housing due 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 were: injection site induration (3% versus 0), site tenderness (10% versus 6%), feeling cold (12% versus 7%), hot flashes (19% versus 12%), hyperhydrosis (15% versus 10%) and nausea (14% versus 2%). Treatment-emergent severe AEs included: a toothache and tooth abscess in two placebo subjects, and a vaginal hemorrhage in a vaccinated subject. One vaccinated subject left due to an exacerbation of pre-existing, but initially undiagnosed, spondyloarthropathy.

Six serious AEs were all deemed unrelated to the vaccine. The three for vaccinated subjects were: cocaine-related paranoia, molar pregnancy resulting in spontaneous abortion in a 42 year old, and alcoholic pancreatitis. The three for placebo 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 over 43 ug/ml (high IgG group), which animal studies indicate are elevated sufficiently to capture enough circulating cocaine to reduce its euphoric effects. [11,12,26] However, only 38% of those vaccinated attained these levels, and these levels were not attained before week eight and then substantially declined between weeks 16 to 24. Both the active and placebo vaccine groups reduced their cocaine use during the first eight weeks probably due to reducing their illicit opiate use through methadone maintenance and CBT. [37–40] Fifty three percent of the high IgG group was abstinent from cocaine more than half the time as compared with only 23% of the subjects who made lesser quantities of antibody in weeks 8–20.

Although not statistically significant, Figure 3 suggests increased use of cocaine in the high IgG group after week 16 when their antibody levels began to fall relatively rapidly, 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.[41,42] While this increased use likely reflects an effort to overcome the anti-cocaine antibody blockade, fortunately, cocaine related AEs did not increase (e.g. overdose, hospitalization) during this interval. Optimal treatment will likely require repeated booster vaccinations to maintain appropriate antibody levels. Furthermore, efforts will be needed in order to retain subjects during the initial series of injections since antibody levels rose slowly over the first three months when patients are immunized according to the protocol used in these studies. Other treatments need to be employed during this early treatment period to encourage abstinence. As an example, to retain subjects in this study during the initial slow rise in antibody responses, we enlisted cocaine dependent subjects who were enrolled in a methadone maintenance program. Methadone patients 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 days/wk) and amount (2–4 dimes/use) of cocaine use (Table 1) were similar to primary cocaine users[4,5,6,8].

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). Nevertheless, it could be argued that a reduction in cocaine use rather than complete abstinence is therapeutically meaningful. Over half (0.53) of the high IgG group showed no new episodes of cocaine use at least 50% of the time (Preston criteria) and doubled their cocaine-free urines from a baseline below 20% to 45%, as shown in Figure 3. Doubling of cocaine-free urines 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 similar population to those in our study.[43] Also, in a double-blinded, placebo controlled human laboratory study, actively vaccinated cocaine dependent subjects who achieved antibody levels of ≥22 ug/ml described a 90% reduction in the effects of 50 mg of smoked cocaine as compared with either their pre-vaccination baseline or when compared 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.[44] Thus, reducing cocaine use can be therapeutically meaningful and is critically dependent on the achievement of appropriate antibody levels.

The rise and decline 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, 45–50]. While the long lived antibody responses described in classical immunology would be desirable, the potent adjuvants (e.g., Complete Freund's Adjuvant) used in experimental animals are too toxic for humans. Using similar numbers of boosters and adjuvants as in our study, both anti-angiotensin and anti-nicotine 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[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.

Acknowledgments

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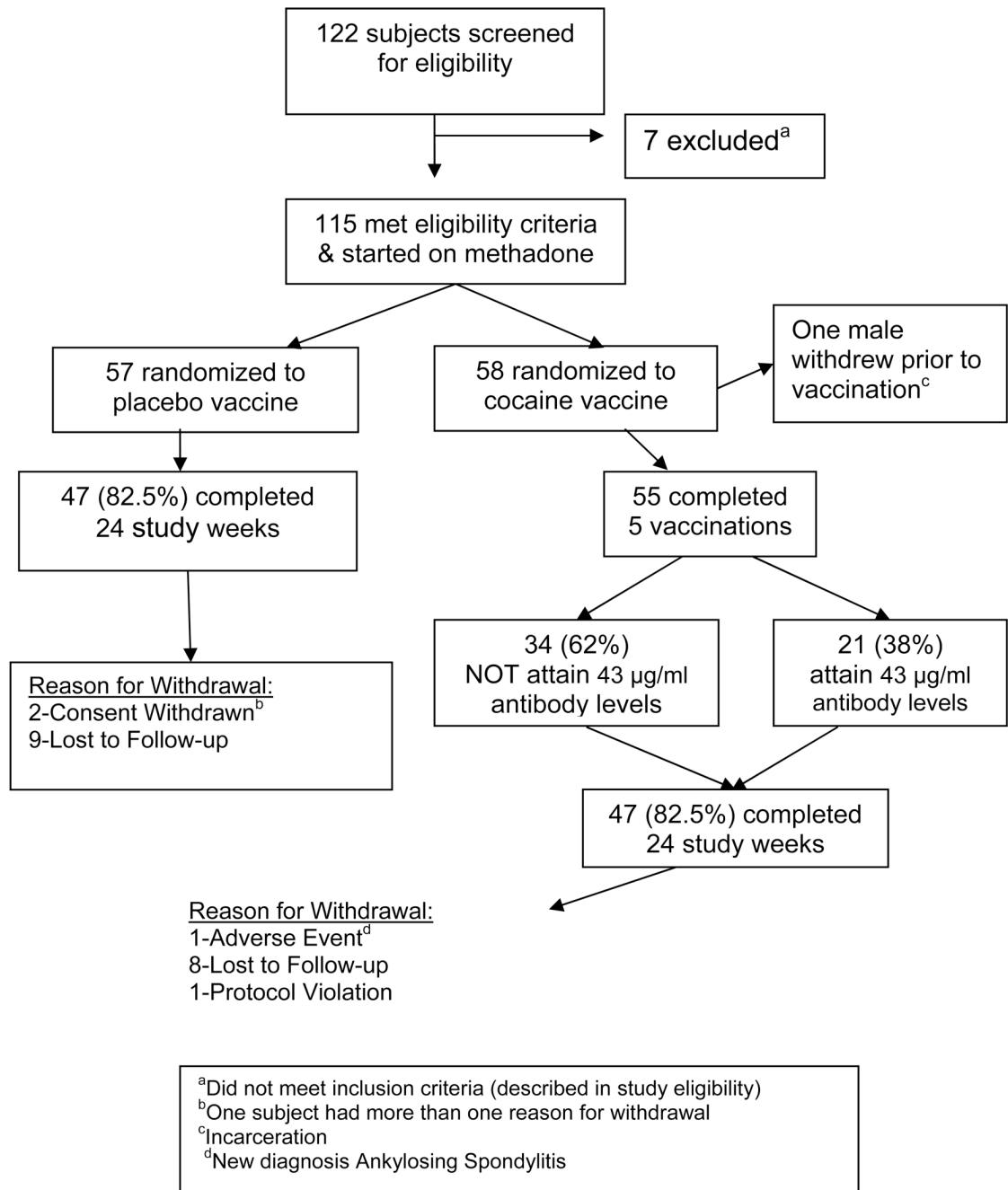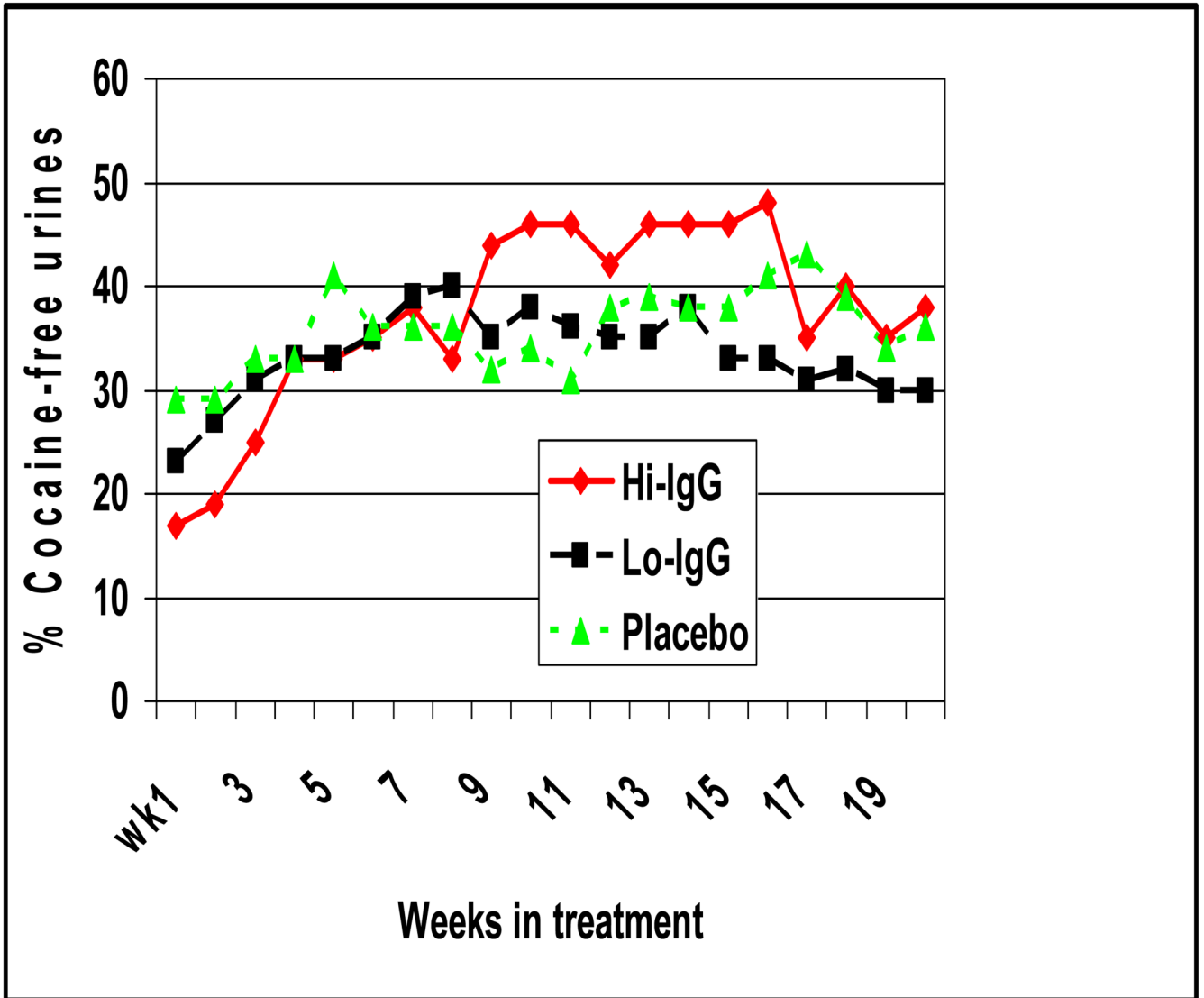
Figure 1.
Flow chart of study participants
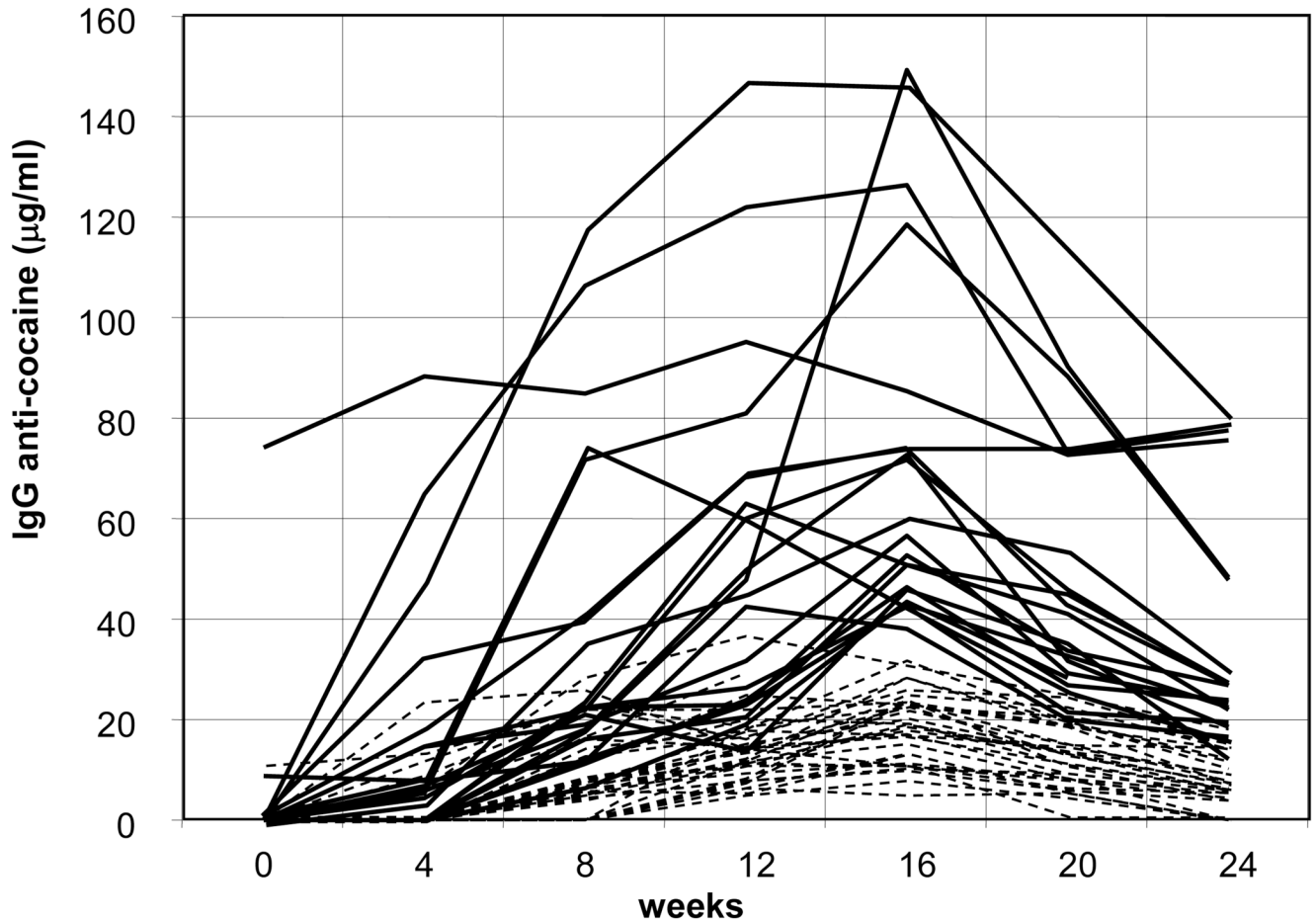
Figure 2. IgG responses to the Cocaine-CTB vaccine was highly variable
Among the 55 immunized with the cocaine vaccine (at weeks 0, 2, 4, 8, and 12), 21 (38%) attained levels greater than 43 µg/ml as shown in solid lines. Of those, 3 three were highly responsive subjects, with one having >60 µg/ml of IgG anti-cocaine antibody even before immunization. Two made a vigorous response after the 2nd injection (week 4 samples). Eight subjects made over 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 anti-cocaine IgG. Antibody responses for the remaining 34 subjects are in dotted lines. The number of subjects at weeks 2, 4, 8, 12, 16, 20, 24 are respectively: 55, 55, 55, 55, 54, 51, 51.

Figure 3. Mean weekly cocaine-free urines by medication condition for weeks 1–20
Green triangles line represents placebo, black squares line active cocaine vaccine recipients with IgG levels below 43 ug/ml (Lo IgG), and red diamonds line active cocaine vaccine recipients with IgG levels > 43 ug/ml (Hi IgG). The x axis is the number of weeks since the first vaccination and the y axis represents 100 times the weekly mean proportion of cocaine-free urines for the three treatment groups. Standard errors are not shown for clarity, but range from +/−5% at any time-point. The Hi IgG group had significantly more cocaine-free urines than the other two groups during weeks 9 to 16 (t=2.26; P<0.03) and a significantly greater increase in cocaine-free urines than the other two groups from weeks 1 to 16 on HLM analysis (Z= 4.8; P<0.01). The three groups did not differ in cocaine-free urines during weeks 17 to 20.
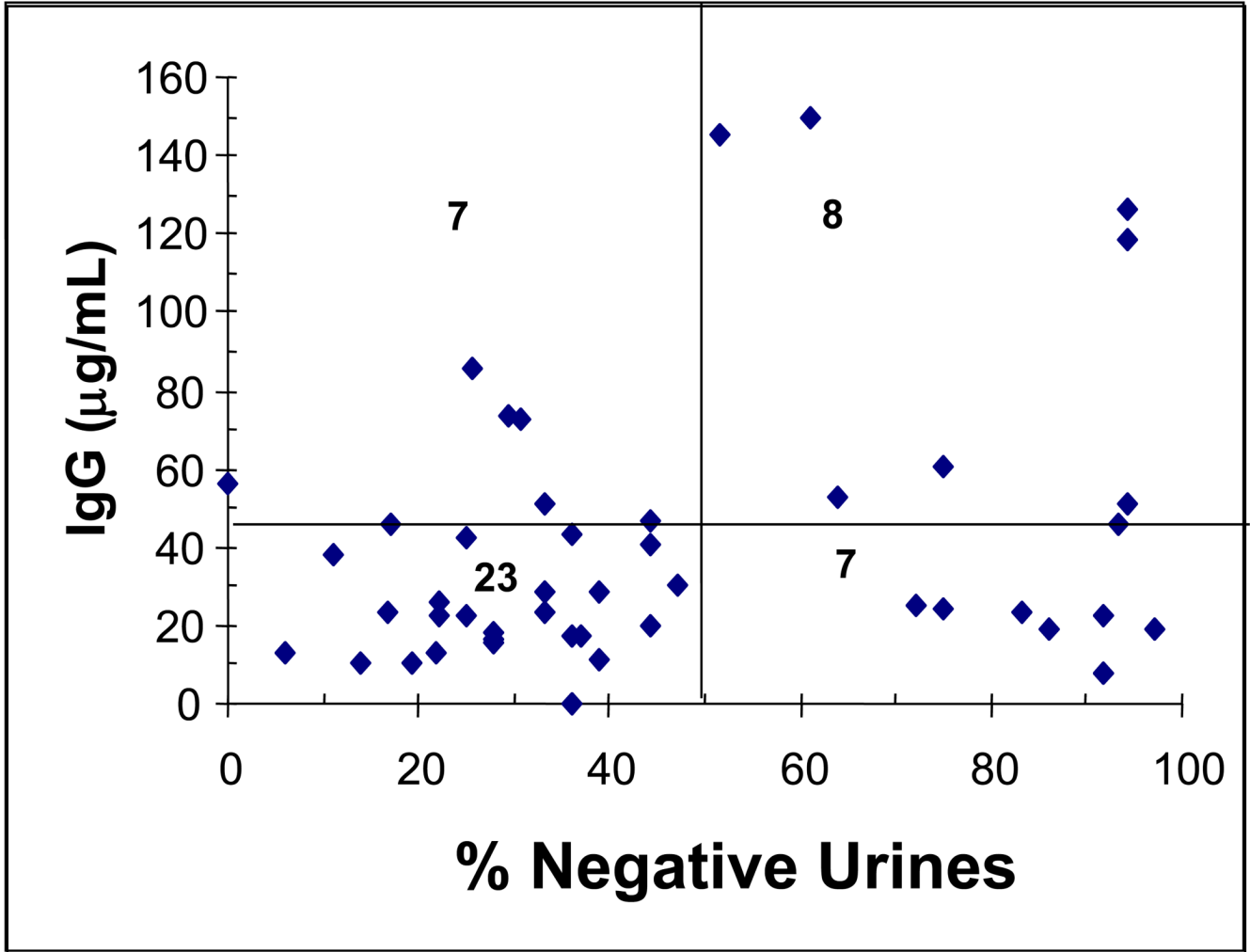
Figure 4. Scatter-plot of peak antibody response by % cocaine-negative urines
Filled diamonds are individual vaccinated subject values for peak antibody response (typically at week 16) plotted against their percentage of cocaine-negative urines using the Preston criteria for new uses of cocaine during weeks 8 through 20. The graph is divided into quadrants by a horizontal line at the 43 ug/ml antibody and a vertical line at 50% cocaine free urines. The numbers in each quadrant represent the number of subjects in each quadrant. The proportion of subjects who had 50% or more cocaine free urines is significantly greater in those with anti-cocaine IgG antibody > 43 ug/ml than those with lower antibody levels (Fishers test, P<0.04).

Table 1

Baseline Clinical Characteristics of Participants[a]

Characteristic	Vaccine	Placebo	P-value
Age (mean ± SD)	35.6 ± 8.9	36.2 ± 9.3	NS
Race [n(%)]			NS
Caucasian	53(93)	46(81)	
African-American	2(3.5)	8(14)	
Mixed[b]	2(3.5)	3(5)	
Sex [n(%)]			NS
Male	35(61.4)	41(71.9)	
Female	22(38.6)	16(28.1)	
Employed	31(54.4)	33(57.9)	NS
Family History of Substance Use	19(33.3)	25(43.9)	NS
Cocaine History			
Age at first use (mean ± SD)	22.1±7.8	20.9±6.1	NS
Days used/week			
Before vaccine	3.3+2.9	2.9+2.8	NS
First 2 wks after vaccine	2.2+2.1	1.9+2.0	NS
Dimes used per day			
Before vaccine	3.5+5.8	2.4+2.7	NS
First 2 wks after vaccine	2.3+2.1	1.7+1.4	NS
Mean $ amount/day on cocaine	$105.00	$77.00	NS
Cocaine Craving[c] (mean + SD)	3.8(2.3)	4.2(2.4)	
Route of Use (%)[d]			
Intranasal	35(61)	36(63)	
Intravenous	14(25)	20(35)	
Smoke	46(81)	41(72)	
Opiate History			
Age at first use (mean ± SD)	23.1±8.1	24.5±12.2	
Amount of Opiates per day			
1–4 Bags	5(10.4)	8(14.5)	
5–9 Bags	17(35.4)	15(27.3)	
10–14 Bags	13(27.1)	11(20)	
15–19 Bags	3(6.3)	6(10.9)	
20–24 Bags	4(8.3)	8(14.5)	
25–30 Bags	2(4.2)	3(5.4)	
> 30 Bags	1(2.1)	1(1.8)	
Unknown	3(6.3)	3(5.4)	
Other Substance Use[d,e]			
Alcohol	8	11	
Non-med prescription use of opioids	27	23	
Cannabis	15	20	

Characteristic	Vaccine	Placebo	*P*-value
Benzodiazapine	2	2	

[a]N=114; Vaccine (n=57); Placebo (n=57)

[b]Option:Caucasian, African-American, Hispanic, Mixed, other

[c]Assessed by the CSSA (Cocaine Selective Severity Assessment) Maximum score=7

[d]Not mutually exclusive categories

[e]By urine toxicology testing from screening (30 days prior to entry) until study completion (14 weeks)

Table 2

Summary of Adverse Events (AEs)

	Placebo (N=57)	Cocaine Vaccine (N=57)	P-value[*]
Number of Subjects with Treatment-Emergent AEs[†]	55 (96.5%)	54 (94.7%)	NS
Number of Subjects with Treatment-Associated AEs[‡]	6 (10.5%)	11 (19.3%)	NS
Total Number of Reports of Treatment-Emergent AEs[†]	417	491	
Total Number of Reports of Treatment-Associated AEs[‡]	9	23	
Number of Subjects Discontinued Due to AEs	0 (0.0%)	1 (1.8%)	NS

[*] P-value was based on the Fisher's exact test.

[†] A treatment-emergent AE was defined as either a new illness with onset date on or after the start of vaccination series, or exacerbation of a pre-existing condition after the start of the vaccination series.

[‡] Treatment-associated AE was an AE that was possibly, probably, or definitely related to the treatment by the Investigator.