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Disulfiram effects on acute cocaine administration

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Abstract

Disulfiram (Antabuse) is being used in outpatient clinical trials to determine its efficacy as a treatment for cocaine dependence. This inpatient randomized, double-blind, placebo-controlled, within-subjects study was conducted to determine whether disulfiram (placebo, 250 or 500 mg/day) alters responses to acute intranasal cocaine (placebo, 1 or 2 mg/kg) administration. Effects of disulfiram on cocaine pharmacokinetics, physiological, and behavioral responses were determined. Disulfiram treatment increased plasma cocaine concentrations three to six times and significantly increased cocaine-associated cardiovascular responses, but did not significantly alter behavioral responses to cocaine. These interactions should be considered in the decision regarding disulfiram treatment in cocaine dependent patients. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Cocaine abuse continues to be a serious public health problem which has defied the development of an effective pharmacotherapy. In addition, the high rate of comorbid cocaine and alcohol abuse has been well-established with prevalence rates for concurrent cocaine and alcohol abuse ranging from 62–90% in the published literature (Weiss et al., 1988; Grant and Harford, 1990). Data from clinical settings indicate that alcohol use can be a behavioral antecedent which is often linked to cocaine abuse (Crosby et al., 1997). A recent study has shown that alcohol pretreatment increased the preference for cocaine over that for a monetary reinforcer indicating that alcohol use may frustrate efforts of patients to reduce or abstain from cocaine use (Higgins et al., 1996). In our clinics, cocaine abusers frequently report that the use of alcohol during a cocaine binge prolongs the cocaine 'high', relieves paranoia and stimulation during the binge, and diminishes acute abstinence symptoms.

Results of recent studies indicate the occurrence of significant morbidity and mortality in association with the detection of both cocaine metabolite and alcohol in individuals (Jatlow et al., 1991; Bailey, 1993). Furthermore, several research groups conducting studies in which single doses of cocaine and alcohol have been administered to volunteers simultaneously have shown substantial increases in cardiovascular responses with the drug combination (Foltin and Fischman, 1988; Perez-Reyes and Jeffcoat, 1992; Farre et al., 1993; McCance-Katz et al., 1993; Higgins et al., 1995). These

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ANOVA, analysis of variance; AUC, area under the plasma concentration–time curve; $T_{1/2}$, elimination half-life; K_{el}, elimination constant; C_l/F, clearance; V_d/F, volume of distribution; T_{max}, observed time to maximum concentration (min); C_{max}, observed maximum concentration (ng/ml).

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studies underscore the potential for significant toxicity with the cocaine–alcohol combination.

In addition to the effects of cocaine and alcohol in humans, an active metabolite, cocaethylene, with cocaine-like pharmacological properties is formed following simultaneous consumption of cocaine and alcohol (Hearn et al., 1991; Woodward et al., 1991; Perez-Reyes and Jeffcoat, 1992; Farre et al., 1993; McCance-Katz et al., 1993). Cocaethylene, the ethyl ester of benzoylecgonine, may play a role in reinforcement and toxicity. Cocaethylene is less potent than equivalent doses of cocaine (Perez-Reyes et al., 1994; McCance et al., 1995), but is eliminated more slowly which could result in its accumulation in the course of binge cocaine and alcohol use. Cocaethylene has been shown to produce a 'high' indistinguishable from that of cocaine and cardiovascular effects similar to those of cocaine (McCance et al., 1995). Toxicity studies in mice have shown that cocaine and cocaethylene are equipotent in producing convulsions and that cocaethylene was slightly, but significantly more potent than cocaine in producing lethality (Katz et al., 1992).

Several investigators have examined an alternate rationale in the search for an effective cocaine pharmacotherapy (Carroll et al., 1993; Van Etten et al., 1994). While typical studies of cocaine pharmacotherapies employ agents intended to decrease cocaine craving or block the 'high', these investigators have tested the hypothesis that preventing the use of alcohol in cocaine dependent patients by treatment with disulfiram (Antabuse), a drug which prevents the metabolism of alcohol and results in a noxious reaction when alcohol is consumed (Fuller and Roth, 1979; Fuller et al., 1986; Wright and Moore, 1990), would decrease cocaine abuse. An added benefit, were such a treatment successful, would be to eliminate any toxicity resulting from the combined use of cocaine and alcohol and cocaethylene formation. Our research group has previously published the results of a pilot study (Hameedi et al., 1995) which examined the effect of one dose of 250 mg disulfiram administered 1 h prior to cocaine administration. This study showed some evidence for an interaction between disulfiram and cocaine in that the peak plasma cocaine concentrations were greater with disulfiram administration. However, well-controlled studies where disulfiram was administered chronically at dosages likely to be used in the clinic have not been reported. Such studies are an important part of drug development in general, and in the case of cocaine pharmacotherapy development, are even more important because of the high risk for relapse to cocaine use in outpatient treatment settings. We report results of a randomized, double-blind, placebo-controlled, within-subjects study which was undertaken to determine the safety and potential efficacy of disulfiram treatment for cocaine abuse.

2. Materials and methods

2.1. Subjects

This study was reviewed and approved by the Yale Human Investigations Committee. Seven volunteers participated (5 African-American, 2 Caucasian; 2 women; age 31.3 ± 2.0 years (mean $\pm$ S.E.)). The subjects in this study were part of a sample for which initial results of disulfiram as a pharmacotherapy for cocaine dependence were recently reported (McCance-Katz et al., 1998). Subjects were non-treatment-seeking and recruited by word-of-mouth or newspaper advertisement. All subjects reported actively abusing cocaine and alcohol at the time of study entry. Cocaine use was confirmed by urine toxicology screens which were collected at each visit during the evaluation process prior to study entry. Subjects were paid for participation in the studies. All identified cocaine as their preferred drug and used by the smoked route. All subjects reported experience with the intranasal route of administration at some point during their cocaine use, and two subjects stated that they continued to use this route intermittently. The mean amount of street cocaine used was 6.1 ± 2.6 g/week. Subjects reported alcohol use primarily during cocaine use, with an average alcohol consumption of 14 ± 13 standard drinks/week (a standard drink = 1.5 ounces of liquor, or 4 ounces of wine, or one 12 ounce beer). Subjects received a comprehensive clinical psychiatric and medical evaluation prior to entry into the study and had no current psychiatric or medical illnesses, nor did they have any significant past history of psychiatric or medical disorders. All subjects met Diagnostic and Statistical Manual of Mental Disorders, 1995 (DSM-IV) criteria for cocaine dependence and alcohol abuse or dependence (none were physiologically dependent on alcohol). Four subjects admitted to occasional marijuana use (1–2 joints/month), but did not meet abuse or dependence criteria for any other illicit drugs.

2.2. Procedures

After giving written, voluntary, informed consent, the subjects were admitted to the inpatient services of either the Yale Psychiatric Institute (which serves as an extension of the General Clinical Research Center at Yale-New Haven Hospital) or the Medications Development Research Center at the Connecticut Mental Health Center, where they resided for the duration of the study. The subjects were instructed to abstain from drug and alcohol use for 3 days prior to admission. Urine for toxicology screen and breathalyzer analysis of alcohol level were obtained on admission. The subjects were monitored clinically for the first 2 days of hospital admission for evidence of alcohol withdrawal, which would have resulted in termination of participation.

2.3. Study design

In this study subjects were hospitalized for 4–5 weeks (based on the requirements of the study protocol and the ability to schedule cocaine administration sessions). The subjects were randomly assigned to each of three blocks of disulfiram treatment (placebo, 250 and 500 mg/day). Subjects received a total of 5 once daily doses of oral disulfiram at 21:00 every evening for each of the three disulfiram study drug blocks. Intranasal (i.n.) cocaine administration studies (three studies for each disulfiram dose; one cocaine session per day) began on the day following receipt of the third disulfiram dose to account for the time necessary for the disulfiram to inhibit aldehyde dehydrogenase (Helander and Carlsson, 1990). Cocaine study drugs included cocaine hydrochloride powder 1 and 2 mg/kg, and a placebo (lactose 2 mg/kg). Lactose was added to the 1 mg/kg cocaine dose in order to preserve the blind. Assignment to cocaine was by limited randomization with the low dose of cocaine always given prior to the high dose of cocaine. Cocaine was presented to the subject on a metal tray from which the subject made lines of drug using a plastic-coated, 2 in. square paper which allowed for the manual manipulation of the drug. The drug was insufflated with a 2 in. straw. The subjects and the clinician raters were blinded to all study drugs. Completion of each block of the cocaine study drug administration sessions was followed by at least 5 days of disulfiram washout. This allowed adequate time for the elimination of disulfiram from the body ($>90\%$ eliminated within 3 days of drug discontinuation) and for new enzyme synthesis (Helander and Carlsson, 1990). Serum cholinesterase activity was determined at study entry and following treatment with each dose of disulfiram.

2.4. Cocaine study drug administration sessions

The drug administration sessions began in the morning, with a baseline physiological and subjective assessment at -30 and -15 min before administration of the cocaine study drug. Blood sampling (by means of an intravenous catheter placed in an arm vein) and physiological monitoring occurred over the next 8 h at time points 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min. Cardiac rhythm monitoring and physiological measures of the heart rate and blood pressure were assessed using automated equipment (Hewlett-Packard 43200A). Cardiac rhythm monitoring occurred for 3 h after cocaine study drug administration and as clinically indicated thereafter. A series of measures designed to assess the subjective drug effects were administered. Visual analog scales consisted of lines anchored at 0 mm = minimal and 100 mm = maximal and measured 'high', 'rush', 'sleepy', 'pleasant', 'nervous', 'paranoid', 'sad, depressed', 'crash', 'cocaine craving', 'good effects' and 'bad effects' (if 'good effects' or 'bad effects' were rated, the subjects were asked to briefly describe such effects).

2.5. Laboratory analyses

Blood samples for analysis of cocaine were collected in gray-stoppered vacutainer tubes which contained sufficient sodium fluoride to prevent degradation of the cocaine by cholinesterase. Samples were immediately centrifuged, the plasma separated and stored at -70 C until the time of analysis. The cocaine concentrations were determined by reverse-phase high performance liquid chromatography with ion pairing, as previously described (Jatlow et al., 1991). The reproducibility (coefficient of variation) for cocaine was less than 5% at concentrations of 100 ng/ml. Serum samples were collected for cholinesterase assay (Kalow and Genst, 1957) before and after the disulfiram study drug treatment.

2.6. Data analysis

Plasma cocaine concentrations were fitted to an open, one compartment model with first order input and elimination using a nonlinear regression computer program with weighted fitting (WinNonlin 1.0™, 1995). The concentrations were weighted according to the reciprocal of the predicted values. The areas under the plasma concentration–time curve (AUC) were calculated using the linear trapezoidal rule and extrapolated to infinity. Kel was derived from the computer fit. Intranasal clearance (C_l/F) and volume of distribution (V_d/F) were determined using traditional non-compartmental methods (Gibaldi and Perrier, 1982). For the pharmacokinetics data, the three disulfiram conditions (placebo, 250 and 500 mg/day) were compared with one another within only the active cocaine conditions (1 and 2 mg/kg).

In a series of preliminary analyses, the simple main effect of the cocaine within the placebo disulfiram condition (i.e. effect of the cocaine alone) was examined with pairwise comparison of each active dose with placebo cocaine (0 versus 1 and 2 mg/kg) as well as each active cocaine dose (1 versus 2 mg/kg). Given the published literature on expected effects of cocaine and to avoid the risk of a type II error, $P < 0.05$ (one-tailed) was considered statistically significant for this small sample.

The AUC values were computed for each dependent cardiovascular and subjective measure under each of the nine study session conditions. All values were analyzed in a series of comparisons done within a two-factor repeated measures analysis of variance (ANOVA). The cocaine dose (placebo, 1 and 2 mg/kg) and the disulfiram dose (placebo, 250 and 500 mg/day) were the independent factors. In the analysis of primary interest,

the simple main effect of the disulfiram within each cocaine dose was determined. Significant simple main effects allowed for the comparison of the disulfiram 250 or 500 mg/day treatment with that of the placebo treatment, as well as for comparison of the two active disulfiram doses (250 versus 500 mg/day). All F ratios with $P < 0.05$ (two-tailed) were considered statistically significant.

Two of the seven subjects withdrew from the study after completion of six of nine study sessions. These subjects experienced negative effects during the cocaine administration sessions, all of which occurred during the second study block when treatment had been with active disulfiram. Because these subjects did not complete the entire study, they were dropped from the analysis and the results are reported for the five subjects who completed the entire study.

3. Results

3.1. Responses to cocaine alone administration

The administration of cocaine alone produced significant increases in heart rate (main effect: $F = 8.79$, d.f. = 2,8, $P = 0.011$, cocaine 1 mg/kg versus placebo $F = 5.87$, d.f. = 1,4, $P = 0.036$, cocaine 2 mg/kg versus placebo $F = 83.89$, d.f. = 1,4, $P = 0.0004$). The cocaine significantly increased systolic blood pressure relative to the placebo administration (main effect: $F = 13.98$, d.f. = 2,8, $P = 0.004$, cocaine 1 mg/kg versus placebo $F = 36.99$, d.f. = 1,4, $P = 0.002$, cocaine 2 mg/kg versus placebo $F = 13.49$, d.f. = 1,4, $P = 0.011$). Diastolic blood pressure increased following active cocaine administration, although not significantly for the cocaine 2 mg/kg dose (main effect: $F = 3.82$, d.f. = 2,8, $P = 0.034$, cocaine 1 mg/kg versus placebo $F = 5.80$, d.f. = 1,4, $P = 0.037$, cocaine 2 mg/kg versus placebo $F = 2.85$, d.f. = 1,4, $P = 0.083$). Active cocaine administration also produced significant ratings of 'high' (main effect: $F = 3.63$, d.f. = 2,8, $P = 0.045$, cocaine 1 mg/kg versus placebo $F = 8.15$, d.f. = 1,4, $P = 0.023$, cocaine 2 mg/kg versus placebo $F = 6.43$, d.f. = 1,4, $P = 0.032$), and 'rush' (main effect: $F = 3.41$, d.f. = 2,8, $P = 0.043$, cocaine 1 mg/kg versus placebo $F = 6.17$, d.f. = 2,8, $P = 0.034$, cocaine 2 mg/kg versus placebo $F = 5.68$, d.f. = 1,4, $P = 0.038$). No statistically significant differences were observed for the comparison of the cocaine 1 mg/kg versus cocaine 2 mg/kg doses for cardiovascular or behavioral effects.

3.2. Responses to cocaine administration following disulfiram treatment

3.2.1. Pharmacokinetics

Following treatment with either dose of disulfiram, the cocaine concentrations were significantly increased as compared to the disulfiram placebo (Fig. 1A and B). AUC (0–480 min) and AUC (infinity) were substantially (3–6 fold) increased, and C_{max} increased 2–3 fold (Table 1). While these markers of cocaine exposure were greater at the higher dose of disulfiram, differences between the disulfiram 250 and 500 mg/day doses did not reach statistical significance with the exception of C_{max} for the cocaine 1 mg/kg administration ($F = 21.16$, d.f. = 1,4, $P = 0.010$). Following the disulfiram treatment, maximal plasma cocaine concentrations occurred later with the T_{max} values following the cocaine 1 mg/kg administration of 96 min (disulfiram 250 mg/day) and 102 min (disulfiram 500 mg/day) as compared to 42 min for the disulfiram placebo, and following cocaine 2 mg/kg administration of 105 min (disulfiram 250 mg/day) and 138 min (disulfiram 500 mg/day) as compared to 48 min for the disulfiram placebo (Table 1, Fig. 1A and B). Compared to the disulfiram placebo, the intranasal cocaine clearance (C_l/F) following cocaine 1 mg/kg was reduced 254 and 416% and V_d/F reduced by 177 and 229% following disulfiram 250 and 500 mg/day, respectively, resulting in plasma elimination half-life increases of 58 and 97% (Table 1). Changes in these parameters tended to be greater at the higher disulfiram dose, but the differences were not statistically significant. Changes in the pharmacokinetics of comparable magnitude were seen with the cocaine 2 mg/kg dose following disulfiram treatment (Table 1). AUCs were approximately proportional to the cocaine dose under each of the disulfiram treatment conditions.

Serum cholinesterase activity was determined prior to the disulfiram treatment and after treatment with disulfiram 250 and disulfiram 500 mg/day. The disulfiram did not appear to alter cholinesterase activity which remained in the normal reference ranges for all subjects under all study conditions (data not shown).

3.2.2. Physiological effects

The physiological parameters monitored following the cocaine study drug administration sessions included the heart rate (Fig. 2A and B), the systolic (Fig. 3A and B) and diastolic blood pressure (Fig. 4A and B). The disulfiram alone treatment significantly increased the heart rate (Table 2), although with this small sample the effect of the 250 and 500 mg/day treatments only approached significance. However, the disulfiram treatment significantly increased the heart rate responses to cocaine (Table 2). The heart rate was greatest following the disulfiram 250 mg/day treatment (Fig. 2A and B), but there was no significant difference between the disulfiram 250 and 500 mg/day treatments. The disulfiram alone treatment had no significant effect on blood pressure (Table 2). Following the disulfiram treatment

Table 1
Summery of the pharmacokinetics effects of disulfiram 250 or 500 mg daily on intranasel cocaine administration

Variable	Cocaine dose (mg/kg)	Placebo	250 mg/day	DS 250 mg/day vs. Pla, d.f. = 1,4 (F, P)	500 mg/day	DS 500 mg/day vs. Pla, d.f. = 1,4 (F, P)	Main effect, d.f. = 2,8 (F, P)
AUC (inf) (ng·min/ml)	1	23448 (2693)*	76201 (17476)	10.18, 0.033	113580 (31918)	8.99, 0.040	7.81, 0.020
	2	41026 (4221)	212145 (51952)	10.57, 0.031	261779 (10511)	609.18, 0.0001	16.52, 0.014
AUC (0-480) (ng·min/ml)	1	2217 (2668)	64147 (14903)	9.40, 0.037	87855 (19997)	13.23, 0.022	11.22, 0.008
	2	39087 (3970)	156675 (35177)	10.65, 0.031	205517 (11624)	302.89, 0.0001	18.83, 0.008
$T_{1/2}$ (min)	1	85 (3.4)	134 (22)	6.13, 0.069	167 (18.3)	27.38, 0.006	7.78, 0.013
	2	90 (4.8)	189 (32.1)	9.12, 0.039	176 (12.7)	29.64, 0.006	6.95, 0.024
C_l/F (l/min per kg)	1	0.0449 (0.00504)	0.0177 (0.00568)	11.68, 0.027	0.0108 (0.00184)	51.34, 0.002	18.20, 0.003
	2	0.0510 (0.00553)	0.0159 (0.00760)	9.67, 0.036	0.0070 (0.00094)	74.48, 0.001	15.70, 0.009
V_d/F	1	5.6 (0.73)	3.1 (0.74)	6.89, 0.059	2.4 (0.29)	32.13, 0.005	10.52, 0.007
	2	6.6 (0.79)	3.0 (0.05)	9.82, 0.035	1.8 (0.31)	45.60, 0.003	18.46, 0.011
T_{max} (min)	1	42 (8.7)	96 (17.5)	8.88, 0.041	102 (12.0)	32.00, 0.005	7.07, 0.022
	2	48 (11.0)	105 (2402)	10.78, 0.030	138 (18.0)	18.95, 0.012	7.59, 0.017
C_{max} (ng/ml)	1	146 (22)	239 (45)	4.52, 0.101	318 (51)	16.83, 0.015	11.29, 0.010
	2	222 (23)	539 (89)	11.71, 0.027	665 (48)	150.25, 0.0003	16.38, 0.005

* Mean (S.E.M.).

Table 2
Summery of the cardiovascular effects of disulfiram 250 or 500 mg daily on intranasel cocaine administration

Variable	Cocaine dose (mg/kg)	Placebo	250 mg/day	DS 250 mg/day vs. Pla, d.f. = 1,4 (F, P)	500 mg/day	DS 500 mg/day vs. Pla, d.f. = 1,4 (F, P)	Main effect, d.f. = 2,8 (F, P)
Heart rate	0	34845 (1897)	37157 (1878)	5.97, 0.071	37004 (1691)	6.66, 0.061	5.12, 0.037
	1	36306 (2045)	40656 (964)	7.92, 0.048	40140 (2148)	20.55, 0.011	6.83, 0.019
	2	37042 (1695)	44556 (1080)	14.41, 0.0.91	41886 (1356)	32.45, 0.005	13.55, 0.012
Systollic blood pressure	0	56381 (2056)	57768 (2280)		59112 (1901)		NS
	1	58635 (1757)	61757 (2015)		62083 (1493)		NS
	2	59046 (1536)	64605 (2018)	17.87, 0.013	64379 (1146)	137.82, 0.0003	14.08, 0.011
Diastollic blood pressure	0	29460 (1442)	30507 (2291)		30905 (1378)		NS
	1	31398 (1129)	32912 (1997)		33297 (1564)		NS
	2	30603 (1546)	33963 (1821)	6.98, 0.057	34668 (1358)	81.09, 0.0008	6.72, 0.049

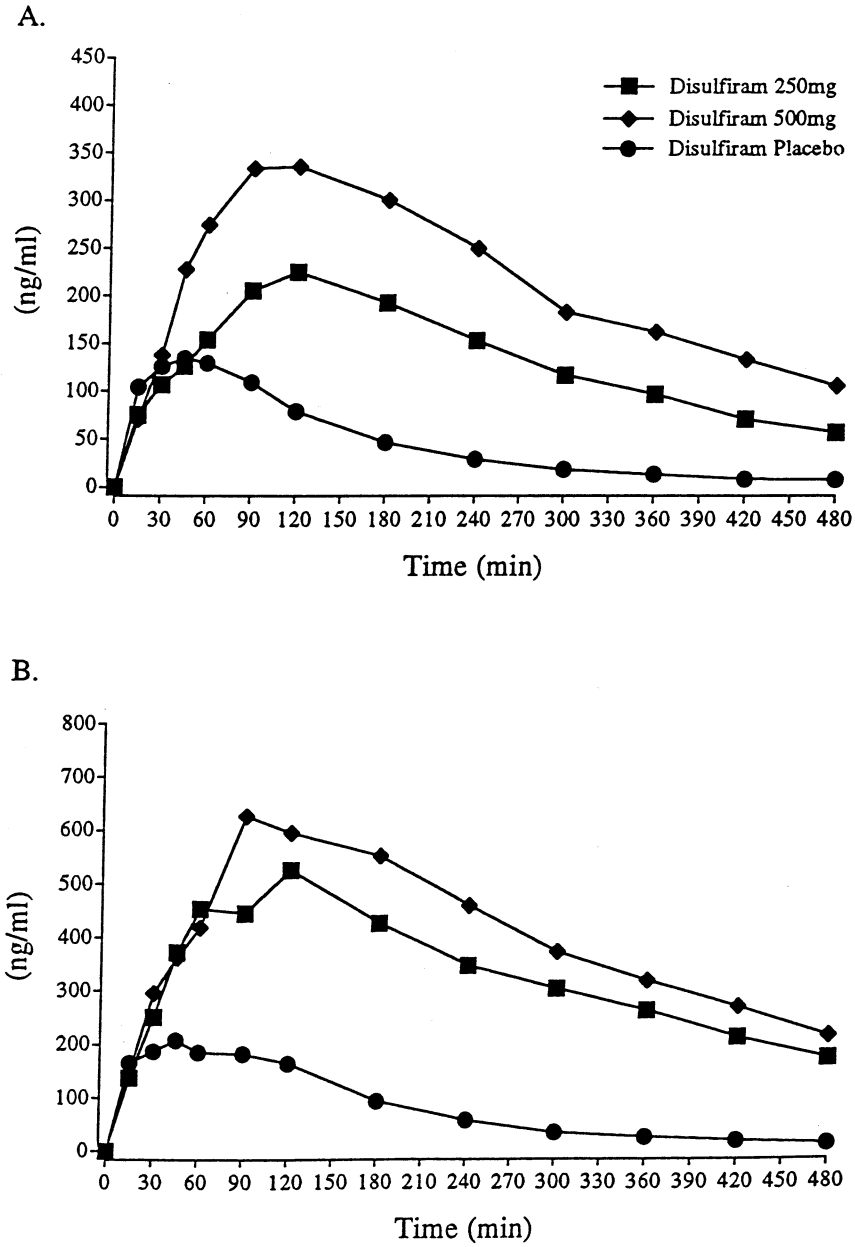

Fig. 1. (A) Mean plasma cocaine concentrations over time following cocaine 1 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day. (B) Mean plasma cocaine concentrations over time following cocaine 2 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day.

the systolic blood pressure (Fig. 3A and B) significantly increased only after the administration of cocaine 2 mg/kg (Table 2). Similarly, following the disulfiram treatment, the diastolic blood pressure (Fig. 4A and B) significantly increased only after the administration of cocaine 2 mg/kg for the disulfiram 500 mg/day treatment and approached significance for the disulfiram 250 mg/day treatment (Table 2). There were no significant differences observed in the effect of the disulfiram 250 versus 500 mg/day treatments on blood pressure following cocaine 2 mg/kg administration.

3.2.3. Behavioral effects

Following the disulfiram treatment and cocaine administration analyses of the ratings for the visual analog scale items 'high', 'rush', 'sleepy', 'pleasant', 'nervous', 'paranoid', 'sad, depressed', 'crash', 'cocaine craving', 'good effects' and 'bad effects' revealed no statistically significant findings. The disulfiram 250 and disulfiram 500 mg/day treatments had no significant effects on any behavioral variables relative to the placebo disulfiram treatment.

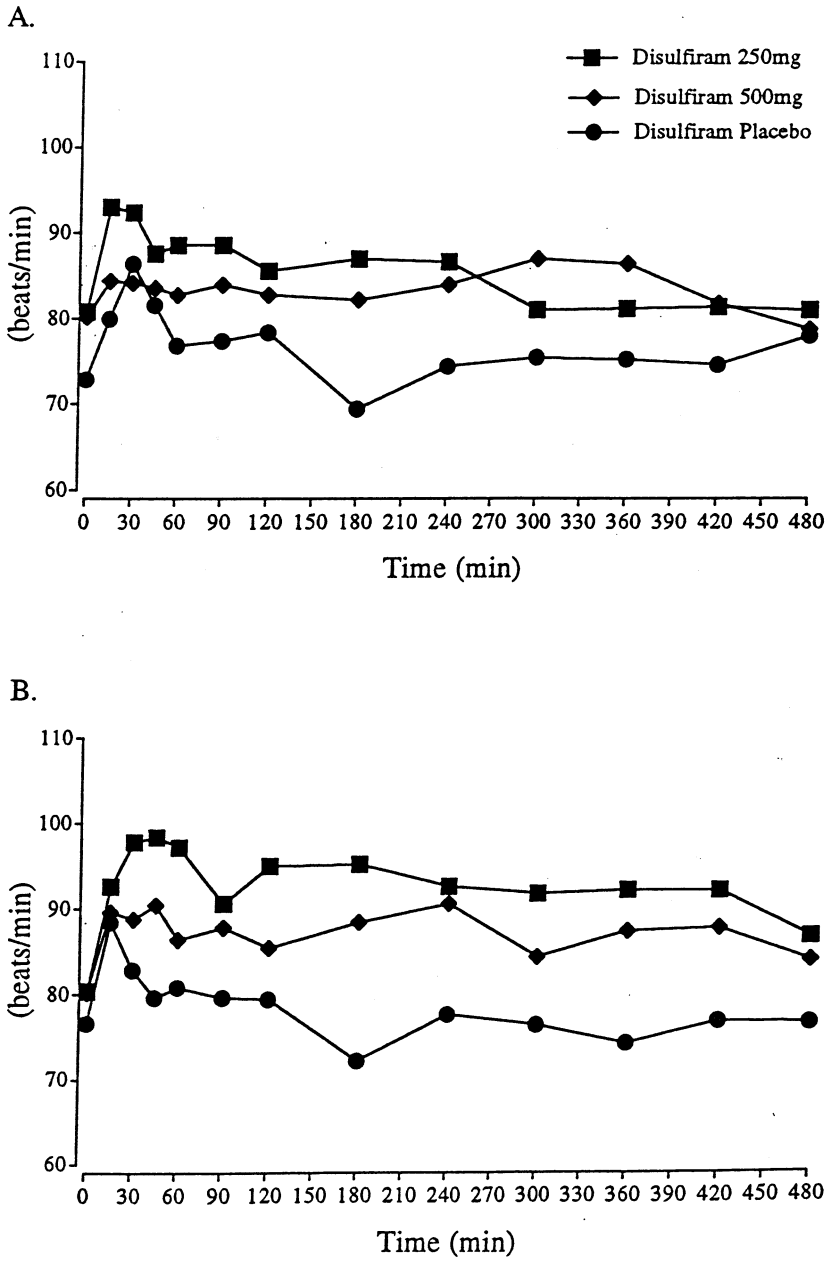

Fig. 2. (A) Mean heart rates (beats/min) over time following cocaine 1 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day. (B) Mean heart rates over time following cocaine 2 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day.

4. Discussion

The results of this study show that disulfiram, at doses regularly used in the treatment of alcoholism, has significant effects on responses to acute intranasal cocaine administration in experienced cocaine users. The disulfiram treatment had a large effect on cocaine exposure characterized by significant increases in AUC and C_{max}. Disulfiram significantly increased cocaine-associated cardiovascular responses, with the greatest effect observed on the heart rate.

When our research group initiated the disulfiram studies we did not suspect that the disulfiram treatment would have such a large effect on cocaine disposition. An early pilot study (Hameedi et al., 1995) in which one dose of disulfiram was followed by cocaine administration and the subjects were followed for only 3 h indicated that the cocaine concentrations were higher following disulfiram administration, but was inadequate to determine the pharmacokinetic parameters or to fully assess the behavioral and physiological responses to cocaine following disulfiram treatment. The present study included longer treatment with disulfiram to better approximate conditions during outpatient treat-

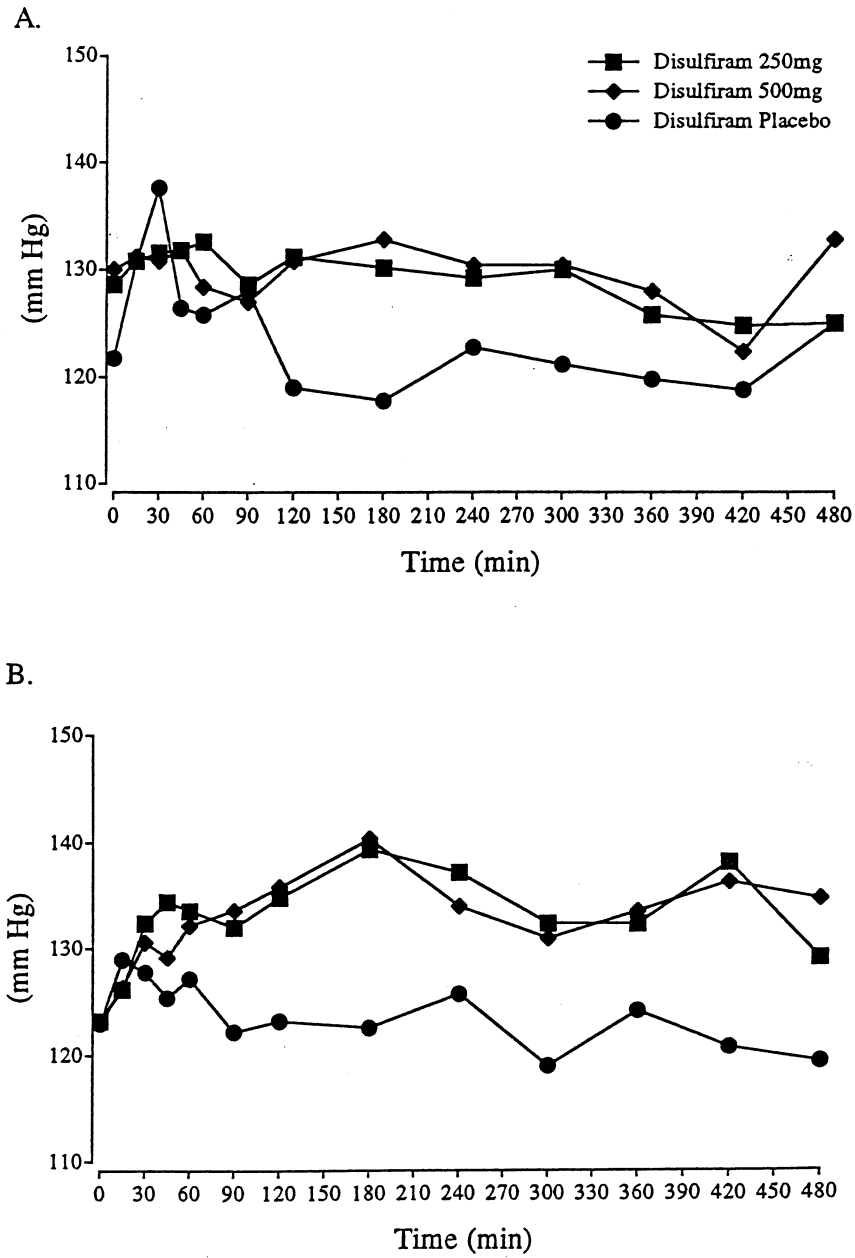

Fig. 3. (A) Mean systolic blood pressures (mmHg) over time following cocaine 1 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day. (B) Mean systolic blood pressures over time following cocaine 2 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day.

ment, a dose-response with limited randomization to the cocaine study drug for safety considerations, and a longer follow-up period after cocaine administration to better define the responses to cocaine during the disulfiram treatment.

Our findings for intranasal cocaine alone administration in this study are similar to those of other investigators who have administered single doses of cocaine by the intranasal route (Van Dyke et al., 1976; Jatlow, 1988; Wilkinson et al., 1988; Jeffcoat et al., 1989) with respect to the pharmacokinetics, underscoring the significant effect of disulfiram on cocaine disposition. There are several possible explanations for the effect of disulfiram on cocaine's disposition. Increased intranasal absorption and reduced metabolic clearance may each have contributed to the observed dramatic increase in the cocaine concentration–time AUC following disulfiram treatment. Disulfiram is reported to decrease the tissue content of catecholamines at the synaptic nerve endings presumably through inhibition of dopamine β-hydroxylase (Goldstein et al., 1964; Mussachio et al., 1964). Normally cocaine absorption through the mucosal route is self-limited as a result of intense local vasoconstriction. Reduced vasoconstriction as a conse-

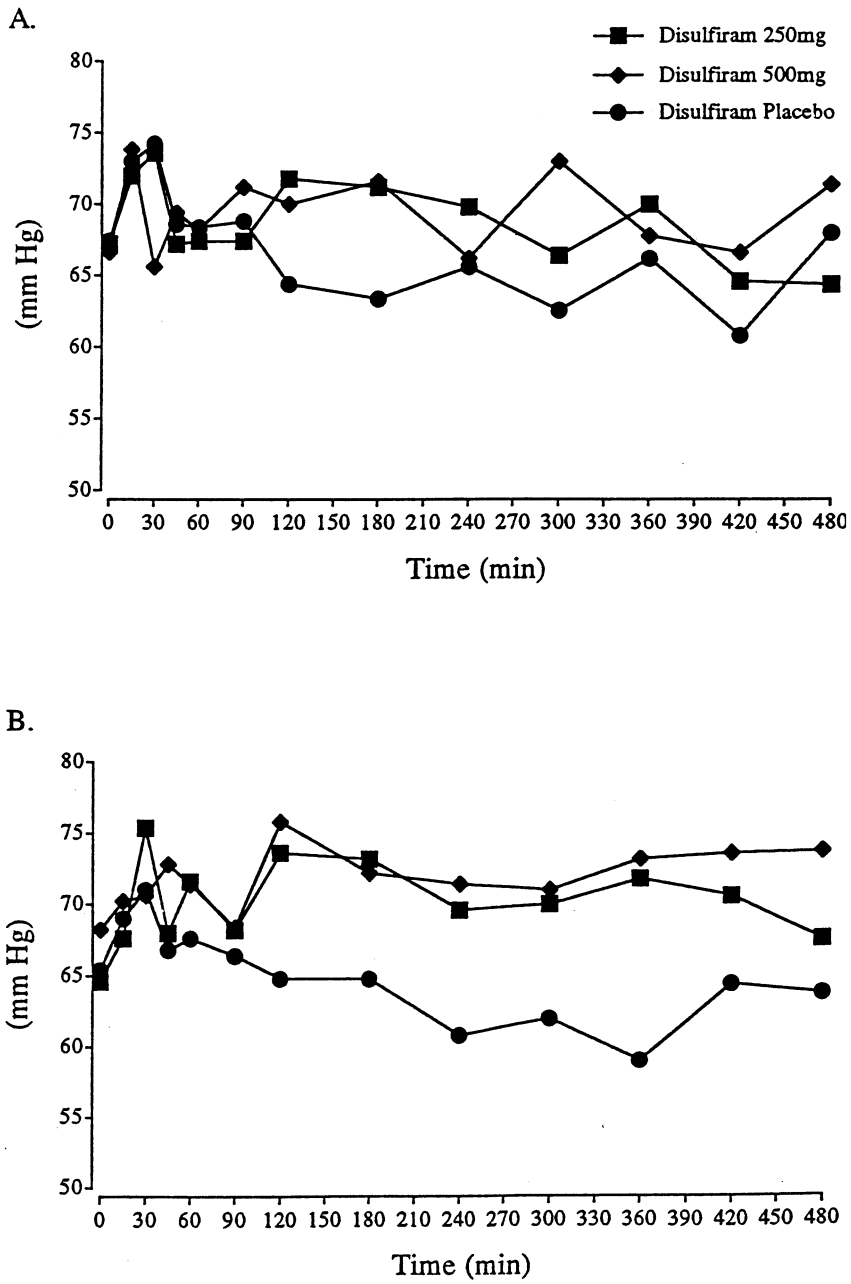

Fig. 4. (A) Mean diastolic blood pressures (mmHg) over time following cocaine 1 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day. (B) Mean diastolic blood pressures over time following cocaine 2 mg/kg administration during treatment with disulfiram placebo, 250, or 500 mg/day.

quence of reduced local norepinephrine concentration might enhance cocaine absorption.

Disulfiram and it's major metabolite, diethyldithiocarbamate, may inhibit cocaine metabolism. Disulfiram is a general inhibitor of aldehyde dehydrogenases (Faiman, 1979; Haley, 1979; Wright and Moore, 1990), and furthermore, has been reported to inhibit both plasma and microsomal carboxylesterases and plasma cholinesterase (Faiman, 1979) which are the primary pathways for cocaine metabolism (Stewart et al., 1979; Benowitz, 1993). Disulfiram and its active metabolite are postulated to inhibit these enzymes by interacting with essential sulfhydryl groups (Faiman, 1979). While the cholinesterase function did not appear to be altered by disulfiram treatment in this study, the assay employed in the laboratory greatly diluted the serum and optimized the assay conditions, and thus might not have detected in vivo inhibition. In addition to the major metabolic pathways which contribute to cocaine metabolism, a minor oxidative pathway of *N*-demethylation of cocaine to norcocaine has been described (Stewart et al., 1979). Oxidative pathways account for approximately 2–6% of the cocaine metabolites (Inaba et al., 1978). Disulfiram has been reported to inhibit

drug demethylation as a result of its ability to competitively inhibit hepatic microsomal drug oxidizing enzymes (Honjo and Netter, 1969). Inhibition of this pathway may also contribute, although probably only minimally, to decreased cocaine disposition.

One of the important findings in this study was the effect of the disulfiram treatment on cardiovascular responses following cocaine administration. The disulfiram alone treatment was found to significantly increase the heart rate; a finding consistent with that of other investigators who showed that disulfiram treatment (100 mg daily for 3 days) increased the heart rate (Sauter et al., 1977). This finding is of clinical importance given the observed interaction of the disulfiram with cocaine. Following the disulfiram treatment, cocaine administration significantly increased the heart rate and the 2 mg/kg dose of cocaine significantly increased the blood pressure over that of the cocaine alone administration. These indices remained elevated even whilst the plasma cocaine concentrations were declining at the later time points. Increases were observed long after that which were observed for the cocaine alone administration.

These findings are in contrast to those obtained by other investigators who have administered multiple doses of cocaine alone to human volunteers and showed evidence for acute tolerance. Ambre et al. (1988) administered an intravenous injection of cocaine and followed this with a cocaine infusion which compensated for clearance over the 4 h study period. They found that the chronotropic (heart rate) effects peaked in 10 min and then declined toward a plateau which was approximately 33% of the peak intensity. Decreased physiological and subjective responses after repeated cocaine doses (by intranasal, intravenous or smoked routes) have been reported (Fischman et al., 1985; Foltin and Fischman, 1991). Foltin et al. (1988) in a study of repeated intranasal cocaine doses found evidence for acute tolerance to the heart rate and the subjective effects of cocaine, but blood pressure increases throughout these sessions resulted in some instances of investigator-initiated termination. Similarly in a study of intravenous cocaine self-administration the initial doses exerted the maximal effects with the subsequent doses exerting much reduced or no effects in the presence of increasing plasma cocaine concentrations, indicating the development of acute tolerance (Fischman and Foltin, 1992). Hatsukami et al. (1994) also observed the development of acute tolerance to the effects of repeated doses of smoked cocaine. One group of investigators has reported no evidence for cardiovascular tolerance to cocaine infusion (Kumor et al., 1988), but this contrasts with the findings of most investigators. The findings in the present study indicate that disulfiram treatment significantly alters the cocaine pharmacokinetics resulting in altered cocaine pharmacodynamics which could have consequences for abusers of street cocaine who engage in binge use of this drug and who are treated with disulfiram.

Whilst the cardiovascular findings in this study remained in a medically safe range, there is potential for increased cocaine toxicity with disulfiram treatment in cocaine-dependent outpatients who relapse and take larger doses of cocaine. Patients with cocaine and/or alcohol related disorders and significant cardiovascular disease should probably not be treated with disulfiram. All patients being considered for this treatment should have a medical evaluation and physical examination to determine whether disulfiram would be an appropriate pharmacotherapy.

While the primary goal of this study was to evaluate the safety of disulfiram treatment for cocaine dependence by determining whether significant interactions occurred with cocaine administration, the question of whether disulfiram alters behavioral responses to cocaine is also of interest. In this study, there were no significant effects of disulfiram on any of the measured behavioral responses to cocaine. We were, however, intrigued by the negative effects reported by some subjects which appeared to be consistent with the accentuation of the stimulant effects of cocaine. Several subjects described a variety of 'bad effects' following cocaine administration during the disulfiram treatment which included dyspepsia/nausea ($n = 3$), palpitations ($n = 2$), anxiety ($n = 5$), and restlessness ($n = 2$). None of these effects required medical intervention, although subjectively, those participants encountering such effects found the experience unpleasant. Two subjects withdrew from the study after experiencing such effects. A much larger sample size would be required to determine whether these effects are related to an interaction between the disulfiram and cocaine, and we opted to terminate this study because of the marked effect of the disulfiram treatment on the cocaine pharmacokinetics and the cardiovascular responses.

One of the limitations of this study is its intranasal route of cocaine administration. All the subjects participating in this study reported smoking as their preferred route of administration. Smoked cocaine produces substantial plasma cocaine concentrations which peak rapidly (within approximately 6 min) as compared to the intranasal route of administration where the maximal plasma concentration occurs at about 45 min (Jeffcoat et al., 1989). The intravenous route of administration also rapidly elevates plasma cocaine concentrations (Javaid et al., 1983; Chow et al., 1985; Jeffcoat et al., 1989) relative to the intranasal route of administration. It is possible that the disulfiram–cocaine interaction could be even greater using these routes of administration.

In light of the findings in this study, and the extrapolation to other routes of administration which might be

expected to increase the effects for the observed interaction, the clinical experience with the use of disulfiram in treatment of cocaine dependence thus far is interesting. Disulfiram is currently being investigated in clinical settings as a treatment for cocaine–alcohol abuse. An open pilot study comparing disulfiram 250 mg/day to naltrexone 50 mg/day found that disulfiram treatment reduced both cocaine and alcohol use and lengthened the periods of abstinence (Carroll et al., 1993). Van Etten et al. (1994) have also reported that disulfiram 250 mg/day decreased cocaine and alcohol use in their patient sample. Subsequently, our research group has conducted an outpatient double-blind, randomized clinical trial ($n = 122$) in which disulfiram 250–500 mg/day was administered in combination with psychotherapy for cocaine dependent, alcohol abusing, patients which showed a beneficial effect of this pharmacotherapy in conjunction with the psychotherapy treatment. The subjects receiving the disulfiram treatment significantly decreased their use of cocaine and alcohol and increased lengths of abstinence were observed. Few adverse events occurred in this study (Carroll et al., 1998).

The present study provides evidence of a significant interaction between cocaine and disulfiram which warrants careful consideration of medical risk prior to initiation of treatment. We plan to undertake new studies in which we will determine whether lower doses of disulfiram might be more efficacious than the doses used in this study. Lower disulfiram doses might have less of an effect on cocaine pharmacokinetics and cardiovascular responses, but still be effective in decreasing cocaine use. Disulfiram might then be a safer drug with which to treat this population at high risk for relapse to cocaine use.

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