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Concurrent cocaine-ethanol ingestion in humans: pharmacology, physiology, behavior, and the role of cocaethylene

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Abstract. Simultaneous abuse of cocaine and ethanol is a common occurrence. Cocaethylene, the ethyl ester of benzoylecgonine, has been detected in the urine of patients reporting concurrent use of cocaine and ethanol, and high levels have been found in the blood of victims of fatal drug overdose. This placebo-controlled, double-blind study examined the pharmacokinetic, physiologic, and behavioral effects of dual cocaine and ethanol administration in humans ($n = 6$). Cocaethylene was found in the plasma only after administration of both cocaine and ethanol, and appeared to be eliminated more slowly than cocaine. Plasma cocaine concentrations were significantly higher during cocaine/ethanol administration. Euphorigenic effects were both enhanced and prolonged, and heart rate was significantly increased, following cocaine/ethanol administration as compared to administration of cocaine or ethanol alone.

Key words: Cocaethylene – Cocaine – Ethanol

The use of cocaine in the United States has reached epidemic proportions, with estimates that 15% of the population have used cocaine at least once and that 3 million persons are chronic cocaine abusers (Abelson and Miller 1988). More recently it has been established that 62–90% of cocaine abusers are also concurrent ethanol abusers (Weiss et al. 1988; Grant and Harford 1990; Rounsaville et al. 1991) and that simultaneous consumption is common.

Cocaine abusers report that use of ethanol during a cocaine binge prolongs the euphorigenic properties of cocaine (the "high") in addition to ameliorating the acutely unpleasant physical and psychological sequelae of cocaine ingestion, primarily paranoia and agitation. The combined use of both drugs appears in some individuals to lessen the dysphoria associated with acute abstinence from cocaine (the "crash"). While these effects could be due to properties inherent to ethanol, recent evidence suggests that a metabolic interaction between cocaine and ethanol results in the formation of an active metabolite (Cami et al. 1991; Hearn et al. 1991; Jatlow et al. 1991).

Cocaethylene, the ethyl ester of benzoylecgonine, has been detected in trace amounts in the urine of individuals with a history of concurrent use of cocaine and ethanol (Rafla and Epstein 1979; Smith 1984). Recent reports have documented the presence of high levels of cocaethylene in blood samples from victims of fatal drug overdose and from emergency room patients who had recently ingested cocaine and ethanol (Hearn et al. 1991; Jatlow et al. 1991). We found that, in some cases, the concentration of cocaethylene was greater than that of cocaine (Jatlow et al. 1991).

The demonstration of high plasma levels of cocaethylene and the implication that this metabolite could contribute to the effects of combined use of cocaine and ethanol, including toxicity, led us to investigate the neurochemical and behavioral effects of cocaethylene (Jatlow et al. 1991). Considerable preclinical neurochemical and behavioral data suggest that cocaethylene is likely to have psychotropic effects in common with cocaine. We have previously shown that like cocaine, cocaethylene binds to the dopamine transporter, blocks dopamine uptake, and causes increased extracellular concentrations of dopamine in the nucleus accumbens following systemic administration. Cocaethylene increases locomotor activity in rats and is self-administered by monkeys. Cocaethylene was found to be equipotent to cocaine with respect to all of these properties, which are characteristic of psychostimulants with abuse potential (Jatlow et al. 1991).

The present investigation was undertaken to evaluate the interaction of cocaine and ethanol in humans and to prospectively document the formation of cocaethylene, using a double-blind, placebo-controlled, within-subjects study design. Pharmacokinetic, physiological, and behavioral parameters of cocaethylene were studied. The possible mechanisms and consequences of combined use of cocaine and ethanol are discussed.

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Materials and methods

Subjects. The design of this study conformed to the Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation prepared by the National Advisory Council on Alcohol Abuse and Alcoholism (1989). Six male volunteer subjects participated (3 African-American, 3 Caucasian; mean ± SD age, 27 ± 4 years). Subjects were either non-treatment-seeking ($n = 2$) and recruited by word-of-mouth or treatment-seeking ($n = 4$) and referred by their drug counselors because of failure in outpatient treatment and need for inpatient treatment. All subjects were actively abusing cocaine and ethanol at the time of study entry. All were offered treatment in a 28-day inpatient substance abuse program available at the Connecticut Mental Health Center upon completion of the study. When clinically indicated, outpatient therapists were involved in inpatient treatment planning and subjects were referred back to the outpatient clinic upon completion of inpatient treatment. Subjects were paid for participation in the cocaine-ethanol administration studies. All six men identified cocaine as their preferred drug and were primarily freebase users, although two admitted to rare intravenous cocaine use. All subjects reported having experience with the intranasal route of administration at some point during their cocaine use, but none administered by this route at the time of admission. The mean amount of cocaine used was 3.7 ± 2.5 g/week. Subjects reported cocaine use to occur 13 ± 7 days per month. Subjects reported ethanol use primarily during cocaine use, with an average ethanol consumption of 41 ± 23 standard drinks/week (standard drink = 1.5 oz liquor or 4 oz wine or one 12 oz beer). All subjects received a comprehensive psychiatric and medical evaluation prior to entry into the study. Medical evaluation included a complete physical and neurological examination, CBC with differential, platelet count, BUN, creatinine, glucose, electrolytes, liver function tests, thyroid function tests, hepatitis profile, HIV antibody, VDRL, plasma cholinesterase activity, routine urinalysis, urine toxicology screen (which had to be positive for cocaine and negative for other street drugs at the time of initial evaluation), and electrocardiogram. All subjects were free of major medical and psychiatric illness. All subjects met DSM-III-R criteria for cocaine dependence or abuse and ethanol abuse. Some subjects admitted to occasional marijuana use (< twice a week), but did not meet abuse or dependence criteria for any other drugs or dependence criteria for ethanol.

Procedures. After giving written voluntary informed consent, subjects were admitted to the inpatient service of the Clinical Neuroscience Research Unit at the Connecticut Mental Health Center, New Haven, CT where they resided for the duration of the study. Subjects were instructed to abstain from drug or ethanol use for 3 days prior to admission. Urine for toxicology screen and breathalyzer analysis of ethanol level were obtained on admission. Both had to be negative to continue in the study. Subjects were monitored clinically for the first 2 days of hospital admission for evidence of ethanol withdrawal, which would have resulted in termination of participation.

Four cocaine/ethanol challenges were administered in a randomized, double-blind sequence to each subject over an 8-day period. The 4 test days included the following drug administration schedule: cocaine (2 mg/kg)/ethanol (1 g/kg); cocaine (2 mg/kg)/ethanol placebo; cocaine placebo/ethanol (1 g/kg); cocaine placebo/ethanol placebo. Cocaine administration was intranasal. Subjects were provided with the prepackaged cocaine study drug (either cocaine hydrochloride powder 2 mg/kg or cocaine placebo (lactose) powder 2 mg/kg), a small rectangular-shaped stainless-steel tray, and a 3-inch straw. Subjects were instructed to insufflate the cocaine study drug using this paraphernalia in the way which was most comfortable for them. This was followed by immediate oral ingestion of the ethanol study drug, either ethanol 1 g/kg (1.1 ml/kg 95% ethanol) in a total volume of 16 oz of a room-temperature, sugar-free, non-caffeinated, carbonated beverage or ethanol placebo (16 oz of the room-temperature, sugar-free, non-caffeinated, carbonated beverage with 2.8 ml 95% ethanol floated on the surface). Comsumption of both substances occurred within a 10-min timespan.

The challenge sessions began in the morning, with a baseline physiological and subjective assessment at − 30 and − 15 min before administration of cocaine and ethanol study drugs. Monitoring occurred over the next 6 h at time points 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, and 360 min. Physiological measures of heart rate and blood pressure were assessed using automated equipment (Dynamap). Cardiac rhythm monitoring (Hewlett-Packard 43200A) was continued throughout the challenge. A series of measures designed to assess subjective drug effects were administered. Visual analog scales included the Self-Rated Analog Scale measuring "high", "rush", "sleepy", "pleasant", and "desire for cocaine" and a second subject-rated version of the High Scale which specifically assessed cocaine "high" (Van Dyke et al. 1982). The "high" item on the Self-Rated Analog Scale asked subjects to rate the overall "high" state without regard to whether the "high" was more similar to that of cocaine or ethanol. The second subject-rated version of the High Scale, on the other hand, specifically asked subjects to rate only the cocaine "high" experienced on the visual analog scale of 0–100 mm, with 0 = "no high", 25 = "almost imperceptible", 50 = "my usual", 75 = "better than my usual cocaine high", and 100 = "better than my best cocaine high". Clinician analog ratings were obtained as an objective measure of the "high" state during all test conditions.

Quantitative analysis of cocaine, cocaethylene, and ethanol. Blood samples for analysis of cocaine, cocaethylene, and ethanol were collected in gray-stoppered vacutainer tubes which contained sufficient sodium fluoride to prevent degradation of cocaine and cocaethylene by cholinesterase and to stabilize ethanol concentrations. Samples were immediately centrifuged, frozen at − 20°C, and at the end of the experiment stored at − 70°C until the time of analysis. Samples were collected at baseline (− 15 min), 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420, and 480 min. Samples were only collected out to 360 min on the first subject, and isolated time points were missed on some subjects.

Cocaine and cocaethylene concentrations were determined by reverse-phase high performance liquid chromatography with ion pairing, as previously described (Jatlow et al. 1991). The primary standard, cocaethylene, and the internal standard, n-propyl cocaine, were synthesized from benzoylecgonine as reported (Jatlow et al. 1991). Reproducibility (coefficients of variation) for cocaine and cocaethylene were each less than 5% at concentrations of 100 and 25 ng/ml, respectively. Ethanol was quantified by gas chromatography with flame ionization detection, employing isopropanol as an internal standard.

Data Analysis. Pharmacokinetic analysis of plasma concentration versus time profiles of cocaine and cocaethylene were performed using an iterative nonlinear regression analysis computer program (PCNONLIN) (Statistical Consultants, Inc. 1986). Based on previous studies of cocaine (Wilkinson et al. 1980), a one-compartment model with first-order input and elimination was selected. Apparent half-life for cocaethylene was also estimated from the slope obtained by linear least squares analysis of the terminal portion (180 or 220 min and subsequent time points) of the plot of log concentration versus time. The elimination rates for ethanol were determined from the terminal slope of a linear plot of concentration versus time assuming zero-order elimination over the concentration range studied. Area under the concentration versus time curve (AUC) for all drugs was determined by the trapezoidal rule, and extrapolated to infinity for cocaine and cocaethylene.

Cardiovascular and subjective responses were analyzed using repeated measures analysis of variance (ANOVA). Drug effects were examined within all test conditions using two-way ANOVA in a Drug × Time model. Huynh-Feldt corrected significance values are reported when the sphericity assumption was not met. Results were considered statistically significant at $P < 0.05$ (two-tailed). For illustrative purposes, magnitude of response was determined for each variable during each of the test conditions and is expressed as peak

change (calculated by subtracting the mean baseline from mean peak level of response) and total AUC with baselines subtracted.

Results

Coadministration of cocaine 2 mg/kg and ethanol 1 g/kg resulted in the formation of cocaethylene in all six subjects (Fig. 1A), but it was not detected during administration of cocaine or ethanol alone. Cocaethylene was initially detected in the 30-min sample (mean ± SEM lag time by computer fit, 24 ± 3 min) at a plasma concentration of 10 ± 4 ng/ml, with peak plasma concentrations of 62 ± 7 ng/ml occurring at 115 ± 9 min. (Fig. 1A and Table 1). Peak cocaethylene concentrations were found to be approximately one fifth those of cocaine (Table 1), but the two were equal by about 360–480 min. The apparent elimination half-life of cocaethylene was estimated by nonlinear computer fit of the entire concentration versus time profile assuming a first-order input function, but attaching no biological significance to the input constant. The value obtained, 148 ± 15 min (Table 1), was essentially identical to linear least squares fit of the terminal portion of the log concentration versus time plot (147 ± 13 min), suggesting that formation of cocaethylene made a negligible contribution to plasma cocaethylene concentrations at these late time points.

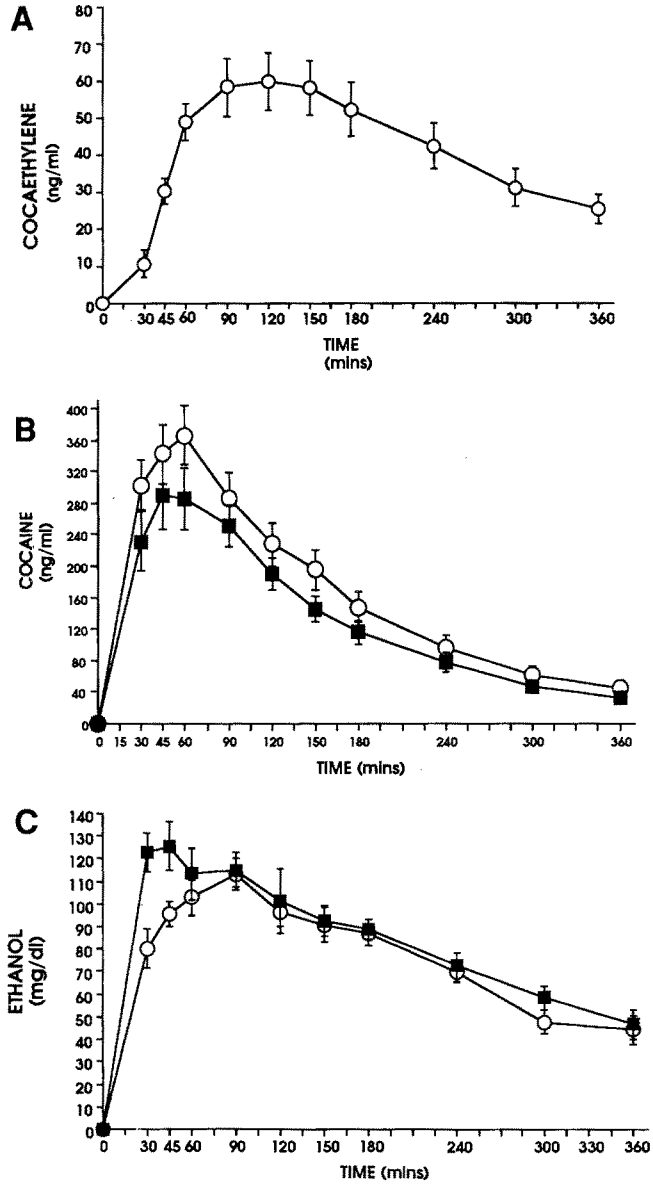

Fig. 1. **A** Plasma cocaethylene levels over time, mean ± SE. (–○–) Cocaine/ethanol. **B** Plasma cocaine levels over time, mean ± SE. (–○–) Cocaine/ethanol. (–■–) cocaine/placebo. **C** Plasma ethanol levels over time, mean ± SE. (–○–) Cocaine/ethanol; (–■–) placebo/ethanol

Peak plasma cocaine concentrations after cocaine/ethanol administration averaged 366 ± 37 ng/ml and occurred at 60 min (Fig. 1B, Table 1), which was significantly higher than was found during cocaine/placebo administration (309 ± 36 ng/ml) (Fig. 1B and Table 1). Plasma cocaine levels during cocaine/ethanol administration were greater than those during cocaine administration alone at each time point, and these differences were statistically significant ($F = 15.58$, $df = 2.69, 50$, $P < 0.001$) (Fig. 1B). The elimination half-lives for cocaine during cocaine/ethanol administration (83 ± 12 min) and during cocaine/placebo administration (86 ± 11 min) were not significantly different (Table 1). The area under the plasma concentration versus time curve for cocaine when followed by ethanol administration was also significantly higher (66 544 ± 7554 ng·min/ml) than for cocaine administration alone (53 992 ± 4516 ng·min/ml).

Ethanol levels and summary statistics are shown in Fig. 1C and Table 1. Plasma ethanol levels during ethanol alone administration peaked at 125 ± 11 mg/dl at 45 min. During administration of cocaine/ethanol, however, the peak plasma ethanol concentration was 113 ± 7 mg/dl at 90 min. Ethanol levels during ethanol alone administration exceeded those during combined cocaine/ethanol administration at each time point, and these differences, while not large, were statistically significant ($F = 3.93$, df = 7.48, 50 $P < 0.002$) (Fig. 1C). Although peak ethanol concentrations were slightly lower in association with cocaine, elimination rates for ethanol with and without cocaine did not differ (14.4 ± 1.4 mg/dl/h and 14.7 ± 0.6 mg/dl/h, respectively).

Physiological parameters (Table 2) monitored during drug administration included heart rate (Fig. 2) and systolic and diastolic blood pressure. The major physiological changes occurred in heart rate during the test sessions that included ingestion of active cocaine. Increased heart rate over that obtained at baseline occurred throughout the cocaine/ethanol test session and peaked at 30 beats per min (Table 2). Heart rate during cocaine/ethanol administration was also significantly increased over that obtained for all other test conditions, including cocaine/placebo (Table 2), as was AUC heart rate response (Table 2, Fig. 2). The increase in heart rate during cocaine/placebo administration occurred during the first 150 min and peak change was 20 beats per min (Table 2, Fig. 2). This increase in heart rate was significantly greater than that during ethanol or placebo administration (Table 2). Blood pressure effects were more variable, and changes during each test condition are summarized in Table 2. Maximal increases in systolic blood pressure

Table 1. Pharmacokinetic measurements of cocaine, ethanol, and cocaethylene (EC) during cocaine ethanol administration

	Cocaine/placebo	Cocaine/ethanol	Placebo/ethanol
Cocaine AUC[a] (ng-min/ml)	53992 ± 4516[b]	66544 ± 7554	0
Ethanol AUC (mg-min/dl)	0	30846 ± 2061	33658 ± 2602
Cocaethylene AUC (ng-min/ml)	0	19361 ± 2509	0
Peak cocaine (ng/ml)	309 ± 36	366 ± 37	0
Peak ethanol (mg/dl)	0	113 ± 7	125 ± 11
Peak cocaethylene (ng/ml)	0	62 ± 7	0
$t_{1/2}$[c] cocaine (min)	86 ± 11	83 ± 12	–
$t_{1/2}$ cocaethylene (min)	–	148 ± 15	–

[a] AUC = Area under the curve
[b] Mean ± standard error of the mean
[c] $t_{1/2}$ = Elimination half-life

Table 2. Physiological responses during cocaine ethanol administration

Assessment	Test condition	Baseline Mean ± SE	Peak change (peak-baseline)	Area under the curve [a] ± SE	Huynh-Feldt corrected significance values ($F = \_$; $df = \_$; $P < \_$)	
					Cocaine/Eth	Cocaine/Pla
Heart rate (beats per min)	Cocaine/Eth	72.25 ± 4.36	30	5861.88 ± 858.09[b]	–	3.44; 10.14, 55; .002
	Cocaine/Pla	71.92 ± 4.82	20	2424.38 ± 1024.75	3.44; 10.14, 55; .002	–
	Pla/Eth	71.25 ± 4.23	7	76.88 ± 655.47	5.97; 7.59, 55; .001	3.60; 11, 55; .001
	Pla/Pla	76.25 ± 1.90	− 0.25	− 1585.63 ± 967.91	4.22; 10.16, 55; .001	4.47; 4.53, 55; .007
Systolic blood pressure (mm Hg)	Cocaine/Eth	126.92 ± 3.49	22.91	2045.63 ± 1092.61[c]	–	NS
	Cocaine/Pla	120.17 ± 2.70	24.33	2967.50 ± 607.72	NS	–
	Pla/Eth	120.42 ± 3.61	3.91	− 1680.63 ± 731.35	NS	3.81; 6.02, 55; .006
	Pla/Pla	118.33 ± 4.44	7.67	12.50 ± 825.60	NS	4.25; 11, 55; .001
Diastolic blood pressure (mm Hg)	Cocaine/Eth	74.08 ± 2.86	7.92	118.13 ± 854.61[c]	–	NS
	Cocaine/Pla	70.67 ± 2.10	2.83	− 331.25 ± 572.96	NS	–
	Pla/Eth	71.92 ± 3.02	− 2.09	− 2085.63 ± 756.68	NS	NS
	Pla/Pla	70.83 ± 1.69	0.34	− 623.75 ± 712.37	NS	NS

NS = not significant
[a] = Area under the curve with baseline subtracted out
[b] = beat. min/min
[c] = mmHg · min

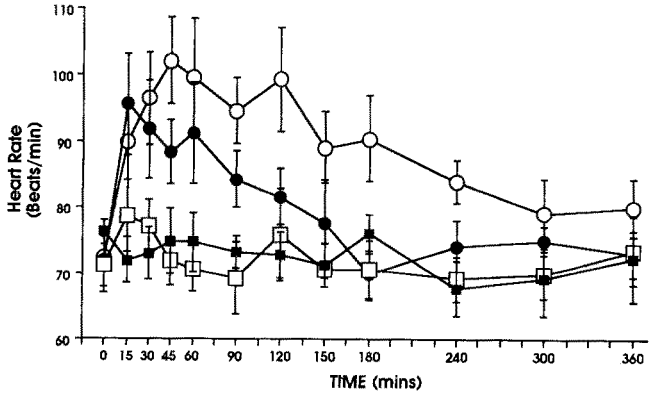

Fig. 2. The effect of cocaine and ethanol, alone or in combination, on heart rate over time, mean ± SE. (–○–) Cocaine/ethanol. (–●–) cocaine/placebo; (–□–) placebo/ethanol; (–■–) placebo/ethanol

occurred during test sessions which included active cocaine administration (Table 2), but did not differ in the presence or absence of ethanol. Statistically significant increases in systolic blood pressure occurred only after cocaine alone administration as compared to ethanol alone ($F = 3.81$, $df = 6.01$, 55, $P < 0.006$) or placebo ($F = 4.25$, $df = 11$, 55, $P < 0.001$). No statistically significant changes in diastolic blood pressure occurred after the administration of any study drug(s) (Table 2).

Results from the High Scale, which specifically measured cocaine "high," are represented graphically in Fig. 3. Statistical comparison of all four test conditions showed significant differences in cocaine "high" ($F = 9.10$, $df = 6.33$, 165, $P < 0.001$). Administration of cocaine/ethanol and cocaine alone produced a cocaine "high", while administration of ethanol alone or placebo produced no perception of cocaine "high" (Table 3). Administration of

Table 3. Behavioral responses during cocaine ethanol administration

Assessment	Test condition	Baseline Mean ± SE	Peak change (peak-baseline)	Area under the curve ± SE	Huynh-Feldt corrected significance values ($F = \_$; $df = \_$; $P < \_$)	
					Cocaine/Eth	Cocaine/Pla
Cocaine high	Cocaine/Eth	0	58.33	6242.5 ± 2635.75	–	2.01; 6.61, 55; .086
	Cocaine/Pla	0	55.5	2461.25 ± 404.73	2.01; 6.61, 55; .086	–
	Pla/Eth	0	0	0	9.10; 5.58, 55; .001	14.64; 2.54, 55; .001
	Pla/Pla	0	0	0	9.10; 5.58, 55; .001	14.64; 2.54, 55; .001
Any high	Cocaine/Eth	0	68.33	6277.5 ± 1615.18	–	6.56; 2.07, 55; .014
	Cocaine/Pla	0	46.17	2052.5 ± 359.21	6.56; 2.07, 55; .014	–
	Pla/Eth	0	41.33	3471.25 ± 1680.00	3.36; 4.36, 55; .025	3.04; 3.37, 55; .053
	Pla/Pla	0	0	0	22.77; 3.32, 55; .001	14.15; 2.79, 55; .001
Rush	Cocaine/Eth	0	29.83	1431.25 ± 702.65	–	NS
	Cocaine/Pla	0	38.17	720.00 ± 197.22	NS	–
	Pla/Eth	0	8.33	125.00 ± 125.00	2.68; 2.94, 55.08	5.45; 2.71, 55; .013
	Pla/Pla	0	0	0	3.32; 2.95, 55; .049	7.33; 1.38, 55; .025

NS = not significant
[a] = Area under the curve with baseline subtracted out
[b] = mm · min

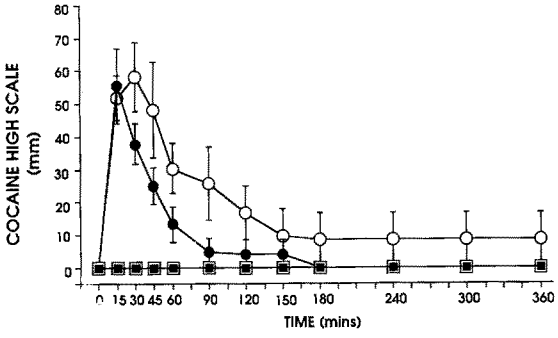

Fig. 3. Cocaine "high" reported over time, mean ± SE. Subjects rated cocaine "high" on a scale of 0–100 mm, with 0 = "no cocaine high", 25 = "almost imperceptible", 50 = "my usual cocaine high", 75 = "equal to my best cocaine high", 100 = "better than my best cocaine high". For symbols see legend of Fig. 2

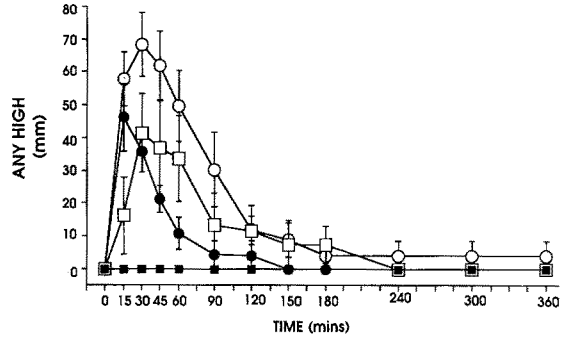

Fig. 4. Any "high" reported over time, mean ± SE. Subjects rated any "high" on a scale of 0–100 mm, without regard to whether the "high" was more similar to cocaine "high" or ethanol "high". For symbols see legend of Fig. 2

both active substances resulted in greater mean values for cocaine "high" at each time point except for the 15 min point as compared to cocaine alone administration. These findings approached statistical significance ($F = 2.01$, $df = 6.61, 55$, $P < 0.086$) (Fig. 3, Table 3). Furthermore, while the cocaine "high" during cocaine alone administration had ended by 180 min, that during cocaine/ethanol administration continued to be reported at 360 min (the termination of the test session) (Fig. 3). Peak cocaine "high" was reported at 15 min during cocaine alone administration and at 30 min during cocaine/ethanol administration (Fig. 3, Table 3).

The "high" item (non-cocaine specific) from the Self-Rated Analog Scale measured the subjective intensity of "any feeling of high" and these results are represented graphically in Fig. 4. Statistically significant differences were found when the four test groups were examined ($F = 7.58$, $df = 9.86, 165$, $P < 0.001$). Administration of cocaine/ethanol produced a greater "high", which was sustained for the entire 360-min test session; this effect was significantly greater than the "high" state reported for the other test conditions (Table 3). The "high" ratings associated with ethanol alone (AUC ethanol "high" response = 3471 ± 1680 mm · min) were actually greater than those for cocaine alone (AUC cocaine "high" response = 2052 ± 359 mm · min) and approached statistical significance ($F = 3.04$, $df = 3.37, 55$, $P < 0.053$) (Table 3, Fig. 4).

In ratings of the item "rush" (sudden onset of intense euphoria associated with the "high" state), statistically significant differences were obtained when the four test groups were compared ($F = 2.93$, $df = 5.23, 165$, $P < 0.03$). Subjects reported peak "rush" occurring at 15 min after cocaine alone or cocaine/ethanol administration (Table 3). Ethanol alone produced low ratings for this variable, with a peak value obtained at 30 min after administration. Cocaine administration was associated with "rush", and these effects were significantly greater than following ethanol administration or placebo administration (Table 3).

Data analyses of ratings for the items "desire for cocaine", "pleasant", and "sleepy" were not statistically

significant. An order effect resulting from administration of cocaine which might result in sensitization to the effects of cocaine on subsequent test days cannot be ruled out because of the small sample size in this pilot study. However, our attempt to minimize this possibility with the use of a randomized design appears to have been successful based on inspection of each individual subject's responses on the 4 test days.

Discussion

This study demonstrates prospectively that cocaethylene is formed after sequential administration of intranasal cocaine and oral ethanol, but not following administration of cocaine or ethanol alone. With the dosage and sequence of administration used in this single-dose study, plasma cocaethylene concentrations were about one-fifth those of cocaine, but AUC of cocaethylene was about one-third that of the parent compound. Apparent elimination half-life of cocaethylene was about double that of cocaine, which was unaffected by ethanol.

These findings take on particular significance given the behavioral effects observed during the four test conditions. Administration of active cocaine and ethanol produced a cocaine "high", which was sustained for a longer period of time than that resulting from cocaine alone. The "any high" state after cocaine/ethanol ingestion was also significantly greater, both in intensity and duration, than that observed after administration of either cocaine or ethanol alone. In fact, ratings on the cocaine High Scale did not rise above baseline following ethanol administration alone, suggesting that the augmented and prolonged response to the combination was not simply an additive effect.

Multiple explanations for the enhanced euphoria associated with the combined consumption of cocaine and ethanol are possible. Jatlow et al. (1991) have found cocaethylene to be similar to cocaine with respect to dopamine uptake inhibition and dopamine release, as well as showing equipotency to cocaine in reinforcement studies in primates. Considerable evidence implicates dopaminergic mechanisms in the reinforcing and euphorigenic actions of cocaine (Roberts et al. 1977, 1980; Pettit et al. 1984; Chiara and Imperato 1990; Kuhar et al. 1990). Cocaine and cocaethylene may have additive effects in humans resulting in enhanced euphoria. Other studies of cocaethylene have shown that its effects on serotonin reuptake and release are significantly less than those of cocaine (Bradberry et al. 1991; Hearn et al.). Some investigators have speculated that serotonin exerts a dampening effect on the euphorigenic property of cocaine (Hearn et al. 1991). If this were true, the combination of cocaine and cocaethylene would be expected to enhance euphoria by increasing the ratio of dopamine to serotonin effects.

Plasma cocaine levels after combined cocaine/ethanol administration were about 30% higher than those during administration of cocaine alone. This may have contributed to the more intense behavioral effects of the cocaine/ethanol administration. The findings for intranasal cocaine alone administration in this study are similar to those of Wilkinson et al. (1980), Jatlow (1988), and Jeffcoat et al. (1989) with respect to its pharmacokinetics and to those of Van Dyke et al. (1982), Fischman et al. (1983), and Higgins et al. (1990) with respect to time course of euphoria ("high"). The mechanism underlying the higher cocaine concentrations observed during cocaine/ethanol administration cannot be determined with certainty from this study. However, ethanol has vasodilating properties (Ritchie 1980) which may allow for increased absorption of cocaine, a potent vasoconstrictor, from the nasal mucosa, which could result in higher cocaine levels. Decreased first-pass hepatic metabolism of cocaine swallowed prior to absorption may also play a role. The elimination constants for cocaine under the two test conditions were similar, which suggests that the higher cocaine levels resulted from increased systemic bioavailability of cocaine following cocaine/ethanol administration. Resolution of this issue would require additional studies using an intravenous route of administration of cocaine and analysis of cocaine's urinary metabolites in the presence and absence of ethanol.

A combined effect of cocaine, ethanol, and cocaethylene may be responsible for the prolongation of subjective effects seen in this study. Cocaine (Kuhar et al. 1990), cocaethylene (Jatlow et al. 1991), and ethanol (Chiara and Imperato 1990) are all known to have mesocortical dopaminergic effects that result in reinforcement of drug administration behavior. In combination, these drugs might be expected to result in enhanced subjective effects reflecting a summation of their individual effects.

Ethanol levels during cocaine/ethanol administration were about 10% lower than those after ingestion of ethanol alone, although elimination rates did not differ significantly and are consistent with those previously reported (Ritchie 1980). While some of the ethanol consumed is utilized in the formation of cocaethylene, this amount is small in comparison to the total dose administered and would not account for the lower ethanol levels observed. The reason for lower ethanol levels following cocaine/ethanol administration is not clear, but one possibility is the decreased absorption of ethanol secondary to local vasoconstriction resulting from the swallowed cocaine after intranasal administration (Cregler and Herbert 1986). Altered metabolism of ethanol in the presence of cocaine and/or cocaethylene cannot be excluded by the current study.

Binge use is a common practice of cocaine abusers (Gawin and Ellinwood, 1988) that has been associated with cocaine-induced cocaine craving (Jaffe et al. 1989). Furthermore, the occurrence of comorbid alcoholism in cocaine abuse or dependence has an estimated point prevalence of 29% and a lifetime prevalence of 62% (Rounsaville et al. 1991). In contrast, comorbid alcoholism with opiate dependence occurs at a much lower lifetime prevalence of 35% (Rounsaville et al. 1991), suggesting that concurrent abuse of ethanol may be an integral component of cocaine abuse. These findings are consistent with the behavioral data obtained in this study documenting the occurrence of enhanced and prolonged subjective effects during combined cocaine and ethanol ingestion. Cocaine/ethanol users frequently report use of

ethanol during a cocaine binge to alleviate acute dysphoric effects of cocaine, including agitation and paranoia ("jitters"). The delayed appearance and longer apparent half-life of cocaethylene observed in this study are consistent with a possible role for this metabolite in ameliorating the acute dysphoric effects of cocaine. Additionally, during binge use of cocaine and ethanol, the level of cocaethylene might eventually exceed that of cocaine. This is particularly important given the recent report of cocaethylene levels which exceeded cocaine levels in four of seven postmortem blood samples from drug overdose victims (Jatlow et al. 1991). Toxicity of cocaethylene alone or in combination with other drugs remains to be established in preclinical studies.

Physiological variables measured during cocaine administration studies have included systolic and diastolic blood pressure and heart rate. The findings in this study agree with those previously reported (Javaid et al. 1978). Peak heart rate increases occurred 15–30 min after intranasal cocaine administration. Heart rate increases were significantly higher during cocaine/ethanol administration than during other test conditions. Systolic blood pressure was significantly increased after cocaine alone administration, but no significant changes in diastolic blood pressure were observed under any of the test conditions. These findings are in agreement with those of Foltin and Fischman (1989), who studied the cardiovascular effects of combined cocaine and ethanol administration in nine healthy volunteers and found that ethanol attenuated the cocaine-induced increase in systolic blood pressure.

The effects of cocaine on cardiovascular indices have been attributed to peripheral norepinephrine uptake inhibition (Fleming et al. 1990). The acute effects of ethanol include increased sympathetic nervous system stimulatory effects (Johnson et al. 1986) and increased cardiovascular reactivity (Zsoter and Sellers 1977). The simultaneous use of these substances might therefore be expected to result in the physiological changes observed in this study. The most common causes of morbidity and mortality associated with cocaine use include myocardial infarction, cerebrovascular accidents, and arrhythmias (Cregler and Herbert 1986; Isner et al. 1986; Gradman 1988). While the toxicity of cocaethylene was not directly assessed in this study, the findings suggest that increased toxicity during cocaine/ethanol ingestion could result from cocaethylene itself, from higher cocaine levels occurring during combined substance use, or from a synergistic adverse cardiovascular effect of cocaine and ethanol in combination.

Implications

The results of this study prospectively confirm that cocaethylene is formed in humans engaging in concurrent use of cocaine and ethanol. The combined use of cocaine and ethanol was associated with enhanced subjective effects which were prolonged relative to those observed during cocaine or ethanol consumption alone. Heart rate was significantly elevated during cocaine/ethanol administration relative to either cocaine or ethanol alone. Our data suggest that cocaethylene may accumulate relative to cocaine during binge use of these drugs. The high prevalence of combined cocaine/ethanol use and the previously reported association of high concentrations of cocaethylene with fatal drug overdose have serious implications for the population at risk. The combined use of cocaine and ethanol would appear to constitute a major public health problem. Indeed, ethanol abuse appears to be an integral component of the phenomenology of cocaine abuse. Dose response and repeated dose studies are of critical importance to an understanding of the relationship of behavioral and physiological effects of combined cocaine and ethanol use, and we are planning to conduct these investigations. Such studies will be useful in developing more effective treatment approaches.

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References

Abelson HI, Miller JD (1988) A decade of trends in cocaine use in the household population. NIDA Res Monogr 61:35–49

Bradberry CW, Murphy E, Nobiletti J, Jatlow P, Roth RH (1991) Comparison of effects of cocaine and cocaethylene on dopamine and serotonin in vivo, using microdialysis. Soc Neurosci Abstr 348 [14]: 888

Cami J, de la Torre R, Farré M, Ortuno J, Segura J (1991) Cocaine-alcohol interaction in healthy volunteers: Plasma metabolic profile including cocaethylene. CPDD Annual Scientific Meeting Abstracts

Chiara GD, Imperato A (1990) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 85:5274–5278

Cregler LL, Herbert M (1986) Medical complications of cocaine abuse. N Engl J Med 315:1495–1500

Fischman MW, Schuster CR, Hatano Y (1983) A comparison of the subjective and cardiovascular effects of cocaine and lidocaine in humans. Pharmacol Biochem Behav 18:123–127

Fleming JA, Byck R, Barash PG (1990) Pharmacology and therapeutic applications of cocaine. Anesthesiology 73:518–531

Foltin RW, Fischman MW (1989) Ethanol and cocaine interactions in humans: cardiovascular consequences. Pharmacol Biochem Behav 31:877–883

Gawin FH, Ellinwood EH (1988) Cocaine and other stimulants-actions, abuse, and treatment. N Engl J Med 318:1173–1182

Gradman AH (1988) Cardiac effects of cocaine. A review. Yale J Biol Med 61:137–147

Grant BF, Harford TC (1990) Current and simultaneous use of alcohol with cocaine: results of a national survey. Drug Alcohol Depend 25:97–104

Hearn WL, Flynn DD, Hime GW, Rose S, Cofino JC, Mantero-Atienza E, Wetli C, Mash DC (1991) Cocaethylene: a unique cocaine metabolite displays high affinity for the dopamine transporter. J Neurochem 56:698–701

Higgins ST, Bickel WK, Hughes JR, Lynn M, Capeless MA, Fenwick JW (1990) Effects of intranasal cocaine on human learning, performance and physiology. Psychopharmacology 102:451–458

Isner JM, Estes M, Thompson PD, Costanzo- Nordin MR, Subramanian R, Miller G, Kastas G, Sweeney K, Sturner WQ (1986). Acute cardiac events temporally related to cocaine abuse. N Engl J Med 315:1438–1443

Jaffe J, Cascella NG, Kumor KM, Sherer MA (1989) Cocaine-induced cocaine craving. Psychopharmacology 97:59–64

Jatlow P (1988) Cocaine: analysis, pharmacokinetics, and metabolic disposition. Yale J Biol Med 61:105–113

Jatlow P, Elsworth JD, Bradberry CW, Winger G, Taylor JR, Russell R, Roth RH (1991) Cocaethylene: a neuropharmacologically active metabolite associated with concurrent cocaine-ethanol ingestion. Life Sci 48:1787–1794

Javaid JI, Fischman MW, Schuster CR, DeKirmenjian H, Davis JM (1978) Cocaine plasma concentrations: relation to physiological and subjective effects in humans. Science 202:227–228

Jeffcoat AR, Perez-Reyes M, Hill JM, Sadler BM, Cook CE (1989) Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking. Drug Metab Dispos 17:153–159

Johnson RH, Eisenhofer G, Lambie GH (1986) The effects of acute and chronic ingestion of ethanol on the autonomic nervous system. Drug Alcohol Depend 18:319–328

Kuhar MJ, Ritz MC, Boja JW (1990) The dopamine hypothesis of the reinforcing properties of cocaine. TINS 14:299–302

Pettit HO, Ettenberg A, Bloom FE, Koob GF (1984) Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology 84:167–173

Rafla FK, Epstein RL (1979) Identification of cocaine and its metabolites in human urine in the presence of ethyl alcohol. J Anal Toxicol 3:59–63

Ritchie JM (1980) The aliphatic alcohols. In: Gilman AG, Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics. Macmillan, New York, pp 376–386

Roberts DC, Corcoran ME, Fibiger HC (1977) On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol Biochem Behav 6:615–620

Roberts DC, Koob GF, Klonoff P, Fibiger HC (1980) Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. Pharmacol Biochem Behav 12:781–787

Rounsaville BJ, Anton SF, Carroll K, Budde D, Prusoff BA, Gawin F (1991) Psychiatric diagnoses of treatment-seeking cocaine abusers. Arch Gen Psychiatry 48:43–51

Smith RM (1984) Ethyl esters of arylhydroxy- and arylhydroxy-methoxycocaines in the urines of simultaneous cocaine and ethanol users. J Anal Toxicol 8:38–42

Statistical Consultants, Inc. (1986) PCNONLIN and NONLIN84: software for the statistical analysis of nonlinear models. Am Statist 40:52

Van Dyke C, Ungerer J, Jatlow P, Barash P, Byck R (1982) Intranasal cocaine: Dose relationships of psychological effects and plasma levels. Int J Psychiatry Med 12:1–13

Weiss RD, Mirin SM, Griffin ML, Michael JL (1988) Psychopathology in cocaine abusers – changing trends. J Nerv Ment Dis 176:719–725

Wilkinson P, Van Dyke C, Jatlow P, Barash P, Byck R (1980) Intranasal and oral cocaine kinetics. Clin Pharmacol Ther 27:386–394

Zsoter TT, Sellers EM (1977) Effect of alcohol on cardiovascular reflexes. J Subst Abuse 38:1–10